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CLOSURE OF ATRIAL SEPTAL DEFECTS

By E. HUSFELDT and H. RAHBEK SØRENSEN

An atrial septal defect is the most common congenital malformation of the heart, very often combined with other lesions. A large defect is a serious abnormality leading gradually to right heart failure, and not infrequently to sudden death. Many attempts have been made during the later years to produce a safe surgical technique for closing atrial septal defects.

In Rigshospitalet, Copenhagen, experiments were started in 1950 with the purpose of developing a simple technique for producing atrial septal defects in dogs (Søndergaard, Rahbek Sørensen, Poulsen & Andersen, 1953) and when this had been accomplished to develop a technique for closing the defects. With the technique which will be described in the present paper it was possible to close experimentally produced defects in 10 dogs without a single death (Søndergaard, Rahbek Sørensen, Poulsen & Andersen, 1953). The technique was demonstrated at the meeting of the »Scandinavian Society for Thoracic Surgery« in Copenhagen in October 1952. It was shortly afterwards used on the first patient and we have at present operated on 12 patients with this technique. The three first cases have been reported by Søndergaard (1953).

Operative technique. The chest is opened through a posterolateral incision with resection of the fifth rib. The superior mediastinum is infiltrated with a solution of 1 % procaine. The pericardium is opened widely in front of the phrenic nerve. The edges of the pericardium are sutured to the chest wall. In front of the right pulmonary veins, behind the right atrium one often sees an area covered with yellow, fatty tissue. Here the pericardium is incised and the heart wall is dissected in order to develop a cleavage between the two atria. If there is an almost total defect, very little can be dissected. If it is a small septal defect, a more than one cm. deep cleavage may be developed. The dissection is carried on behind the superior and inferior caval veins which previously have been completely freed and at intervals are retracted by means of a heavy silk ligature layed around the veins.

The left index finger is now introduced through the right auricular appendage into the right auricle. The defect is explored and also the cava veins, the pulmonary veins, the tricuspid valve and the mitral valve. If the atrial septal defect is accompanied by a mitral stenosis (Lutembacher's disease) a valvulotomy of the mitral valve may be performed through the atrial defect. Guided by the finger in the right atrium one silk suture No. 10 is anchored in the upper edge of the ventricular septum just in front of the aorta at the upper end of the cleavage and another silk suture is anchored in the ventricular wall below the atrioventricular sulcus under the inferior cava vein. The long ends of these two silk sutures are taken behind the superior and inferior cava veins and tied over a piece of gelfoam placed in the cleavage between the two atria. This pulls the atrial septum or what remains of it down against the upper edge of the ventricular septum, thus functionally closing the atrial septal defect.

Clinical experience. 12 patients have been operated upon by June 1954. There were 9 females and 3 males aged from 4 to 39 years. The *Roentgen examination* were in all cases characteristic of an atrial septal defect: the heart was enlarged, the pulmonary artery prominent and the lungs full of blood. The *electrocardiogram*

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showed a right axis deviation and various variations in the conduction system. The *stethoscopy* revealed a systolic murmur in all cases. Two patients had developed stasis of the liver.

The diagnosis has in all cases been confirmed by heart catheterization in the Medical department B (Professor E. Warburg) and an arteriovenous shunt has been demonstrated. In the majority of the cases the defect has been catheterized directly.

Symptoms: All the patients have suffered from functional dyspnoea varying from moderate to very pronounced, and in all cases this has been progressing prior to the admission to the hospital. Some patients have suffered from palpitations and others from attacks of cyanosis.

Table 1.
Results of operation.

	Sex	Age Years	Size of defect	
			Before operation	After operation
1	male	5	> 3 cm	< 1 cm
2	female	4	total	< 1 cm
3	female	12	total	1—2 cm
4	female	28	almost total	< 1 cm
5	female	12	almost total	< 1 cm
6	female	39	almost total	1 cm
7	male	31	3 cm	closed
8	female	11	1 cm	closed
9	female	14	almost total	closed
10	female	15	almost total	closed
11	male	8	total	½ × 1 cm
12	female	4	almost total	died on table

Operative results (table 1): In the first 4 cases the finger was not introduced into the atrium and the size of the defect was determined by invaginating the appendage and the atrial wall before and after the suture was tied. 9 of the defects have been total or almost total. Two of these have been closed completely, four have been reduced to a diameter of less than one cm. and in one case the diameter was reduced to between one and two cm. The size of these defects is so small that they physiologically are of no importance. Two smaller defects have been completely closed and one having a diameter of more than 3 cm., was reduced to less than 1 cm.

There were two postoperative death. One patient (case 2) died 24 hours after the operation of heart failure and the autopsi showed that the mitral and tricuspid valves were defectiv and incompetent. Another case (case 12) developed right heart failure during the operation and died on the table. The autopsy showed a subtotal atrial septal defect going one cm. down into the ventricular septum, which seemed to make the tricuspid and mitral valves incompetent.

There was one case of total heart block (4—1 block) which disappeared before the patient left the hospital. Several patients had tachycardia for a long time and slightly elevated temperature during 2—4 weeks.

Improvement was generally obvious before the patients left the hospital, and in some cases the heart shadow was markedly reduced, but it is too early to evaluate the lasting results. Case 1 improved after the operation, but died 9 months later from pertussis, sepsis and endocarditis. Case 3 is leading a complete normal life one year after the operation. In case 4 the progression of the disease has been checked and the patients dyspnoea is so little pronounced that she is able to manage her house with a little help.

CONCLUSION

A technique has been developed by which one can close or markedly reduce even total atrial septal defects. The technique has the advantage over technically more difficult methods (Cohn 1947, Swan et al. 1950, Gross et al. 1952, Bailey et al. 1953) that it can be applied also to total defects. In cases complicated by abnormally entering pulmonary veins one may perform a lobectomy as in our case 8, or use the technique described by Bailey et al. which we have used successfully in 3 cases which do not come into this series.

The technique described in this paper seems to carry a comparatively low mortality which should justify its application even in cases with less pronounced symptoms, where the damage to the heart is not yet irreparable.

SUMMARY

A technique for closing atrial septal defects is described. 12 patients have been operated upon of whom 9 had total or subtotal defects. The defects have been closed or reduced to a size which is of no physiological importance. There were two postoperative deaths, and in those cases the autopsies showed complicating malformations of the tricuspid and mitral valves.

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COMBINED TREATMENT OF OSTEOSARCOMATA WITH ROENTGEN RAYS AND RAW EGG YOLK

A PRELIMINARY REPORT ON RESULTS OBTAINED IN CHILDREN AND ADULTS

By CARL KREBS

Osteosarcoma has always been regarded as an absolutely hopeless disease, both in children and adults. Certain forms of osteosarcoma are claimed to be less malignent and slower of growth than others, but it is nevertheless a fact that all patients who were treated for that disease at the Radium Centre for Jutland, Århus, within the period 1937—1950 have succumbed. During these 14 years, a total of 31 patients with osteosarcomata were treated with roentgen irradiation; the duration of survival, reckoned from the day of admission, ranged from 461 to 4 days and averaged 250 days.

Irrespective of the histological type, osteosarcoma is a disease which demands the greatest attention, and attempts must be made to improve the results of treatment, even if this is done by leaving the beaten track.

Surgical measures have been given a trial, but although the operative treatment used during recent years is far more radical than earlier, this does not seem to have resulted in an essentially better prognosis.

The principle of the method described in this and previous papers on the same subject (2, 3, 4, 5) is based on the observation that the growth of these bone tumours is frequently arrested by the epiphyseal line.

It is with considerable anxiety that I publish this case material, which consists of only a relatively small series of patients, but I find that this combined therapy has given results which are better than any I have previously seen. It is of great importance to collect a larger and well-analyzed case material in order to form a final opinion on the possibilities of the method, and I cherish the hope that other investigators will take up research work on this problem.

In experimental clinical work on osteosarcoma, which is at once a highly variable and comparatively rare disease, many years will elapse before it is possible to give a definite opinion on the results obtained and to make a careful classification of the case material on the basis of clinical, histological and radiological observations.

All investigators who have studied and treated osteosarcomata in children know that the growth of the tumour tissue, despite its immense destructive and invasive power, is very often arrested by the epiphyseal line. The tumour may without difficulty penetrate fasciae, muscles, bones, nerves and vessels, but the soft, vascular epiphyseal line usually forms a barrier to its further penetration.

It would seem easy for the tumour to penetrate the epiphyseal line, but the impenetrability may be due just to the soft tissue of the epiphyseal line and its function.

It is a well-known fact that granulation tissue possesses a very strong bactericidal action. When an interval of 6—7 days has been allowed to elapse, it is impossible, or nearly impossible, to infect a granulating wound.

On two occasions, I have in patients with vulval cancer who had been subjected to electrocoagulation observed tumour tissue which like exuberant granulation tissue grew across freshly granulated surfaces, but the cancer did not infiltrate into the deeper layers. Incidentally, the cancer disappeared after administration of minimum doses of irradiation.

It is not easy to determine the cause of this phenomenon, but both in granulation tissue and in epiphyseal lines there are either embryonal or undifferentiated cells which are capable of preventing the infiltration of foreign tissue, possibly because of their content of growth-stimulating substances.

In the treatment of a 12-year-old boy, who in 1930 was admitted with an osteogenic sarcoma of the lower end of the right femur, I saw very distinctly how powerful a barrier the epiphyseal line may form against penetration. Intense roentgen irradiation was given, but in spite of this, eight weeks later the tumour had spread like wildfire beneath the periosteum and throughout the bone marrow, but neither the peripheral nor the proximal epiphyseal line was crossed (for roentgenograms, see (3)).

At that time, I tried the effect of injections containing scrapings from the epiphyses of calves. Unfortunately, I did not master the technique involved, and my experiments proved unsuccessful.

During the 25 years which have passed since then, a vast number of substances have seen the light: hormones, vitamins, substances accelerating the deposition of calcium, and substances which

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may stimulate a resting tendency in the cell to deposit calcium.

Sarcoma cells have presumably preserved a tendency to secrete intercellular substances, and those of the osteosarcoma also a tendency to deposit calcium. That this is the case, appears from the fact that it is not a rare occurrence to see deposits of calcium or, perhaps, of osseous tissue in metastases in patients with osteosarcomata, and it is this tendency I have attempted to utilize by administering egg yolk.

Since a fertilized egg possesses the power of developing into a chicken in the course of three weeks, the egg yolk must contain all the substances which are necessary for the formation of the various organs, including bones.

If egg yolk exerts an action which may somehow be useful in the treatment of osteosarcomata, it would seem most reasonable to use absolutely fresh eggs with a large content of vitamins, as but little is known about the substances which may be active in the yolk. Obviously, preserved eggs cannot be used.

After the appearance of the first report in Ugeskrift for Læger, I have learnt that others have attempted to treat patients with osteosarcomata with raw eggs bought in ordinary provision shops.

The eggs we use in the treatment are obtained from a special poultry farm, which we inspect at frequent intervals. The hens' food consists of barley, oats and wheat supplemented with grated carrots, ensiled herrings and freshly crushed common mussels (Mytilus edulis). The mussels (still with shells) are crushed and included in the food every second day, and any leavings are removed the next day, because we consider it of importance that the mussels are absolutely fresh. For the same reason, mussels which have opened before the crushing are discarded. After the lapse of a few days the hens swallow the mussels eagerly.

The reason why common mussels were chosen as a supplementary food is that these animals must be supposed to contain substances which are apt to induce increased deposition of calcium. However, in my opinion, it is, above all, important that only newlaid eggs are used. The eggs we give our hospitalized patients are never more than 48 hours, while those we send to out-patients may be up to 72 hours old.

Numerous determinations of the hatchability of fertilized eggs have been carried out. In a very comprehensive study, T a i l o r showed that in eggs stored under practically the same conditions as are used in this country the hatchability was reduced to zero after the lapse of 28 days. Other studies show that the viability of chick embryos in fertilized eggs is essentially the same or slightly decreasing during the first 10 days, whereas it has decreased to 0—25 per cent. after the lapse of 4 weeks.

Before I compare the present results with those we have previously obtained, I want to emphasize that osteosarcomata have always been given the greatest attention in our programme of treatment at the Radium Centre.

As early as 1927, I began to use fractionated roentgen irradiation in the treatment of osteosarcomata (K r e b s (1)). As already mentioned, during the next few years I tried to see if injections containing scrapings from epiphyses of calves had any beneficial effect on patients with osteosarcomata, but the experiments resulted only in infections. In subsequent experiments, I investigated if the blood had any effect. Two or, sometimes, three times a week, 500 ml. of blood was withdrawn from patients with osteosarcomata and replaced by the same amount from healthy subjects. The patients were followed with the greatest interest from day to day, and the roentgen treatment was, of course, given with meticulous care. As the patients have always been regarded as hopeless cases, I find that it is more justified than would otherwise have been the case to compare our previous results with those obtained after the introduction of raw egg yolk in the treatment of such patients.

For the purpose of analyzing the results I have divided the patients into uniform groups and calculated the duration of survival from the day of admission to July 1, 1954, or to the day of death.

The group of patients which may be of the greatest interest comprises children under 18 years of age with sarcomata of the extremities. These sarcomata fulfil the classic requirements made on the diagnosis by the surgeons, viz.: —

1. localization,
2. destruction,
3. periosteal reaction,
4. spicule formation, and
5. soft-part swelling.

An additional requirement was either an unquestionable histological diagnosis, the presence of metastases, or (in the few patients in whom the histological examination failed although the diagnosis was unmistakable, and who were discharged at request and later died at home) continued growth of the tumour with fatal termination.

Statistics may be deceptive, especially, as is the case here, when a comparatively small number of instances is considered, but nevertheless I find that the accompanying diagrams give an impression of the results of treatment. I do not want to give an impression which is too optimistic, for nothing is more disappointing and difficult than the treatment of osteosarcomata or, on the whole, of sarcomata. One day one may feel elated and cheerful and the next day be deeply disappointed. There is scarcely any task which is so disheartening as that of treating children suffering from such a disease.

For the purpose of the construction of the diagrams I classified the patients according to various principles, viz. patients over and under 18 years af age; patients with Ewing's sarcomata; a more mixed group which I have termed osteogenic sarcomata; finally, all the patients were considered collectively in one large group.

A total of 10 patients under and 16 patients over 18 years of age were treated.

It seems as if the general condition of the patients who were treated after the introduction of egg-yolk therapy was just as good or, rather, just as poor as had previously been the case. The patients were just as weak when they were admitted, and just as many had spontaneous fractures and metastases as before, and it applies to all of them that they did not present themselves for treatment at an earlier stage than had previously been the case.

The first diagram (fig. 1) shows the duration of survival for patients with osteosarcomata of the extremities under 18 years of age. Each column represent a patient. The abscissa shows the number of patients and the ordinate the duration of survival. The patients are placed in chronological order. The group to the left were treated with roentgen irradiation only, while those to the right received roentgen therapy and raw egg yolk.

The next diagram (fig. 2) shows the duration of survival for all patients with osteosarcomata under 18 years of age. It will be seen that five of the 10 patients who were given raw egg yolk are still alive.

The diagram in figure 3 shows all patients with sarcomata of the extremities, children as well as adults. Also here, the duration of survival

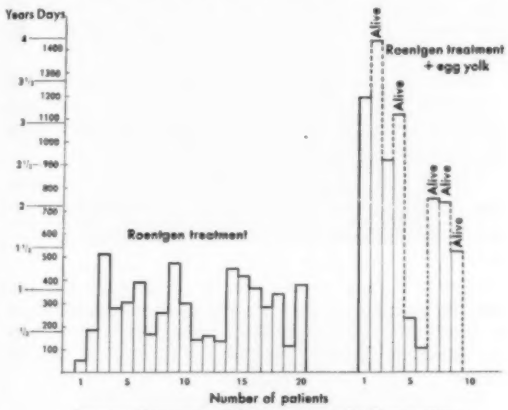

Fig. 1.

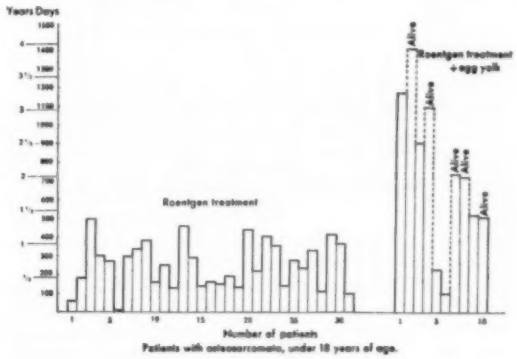

Fig. 2.

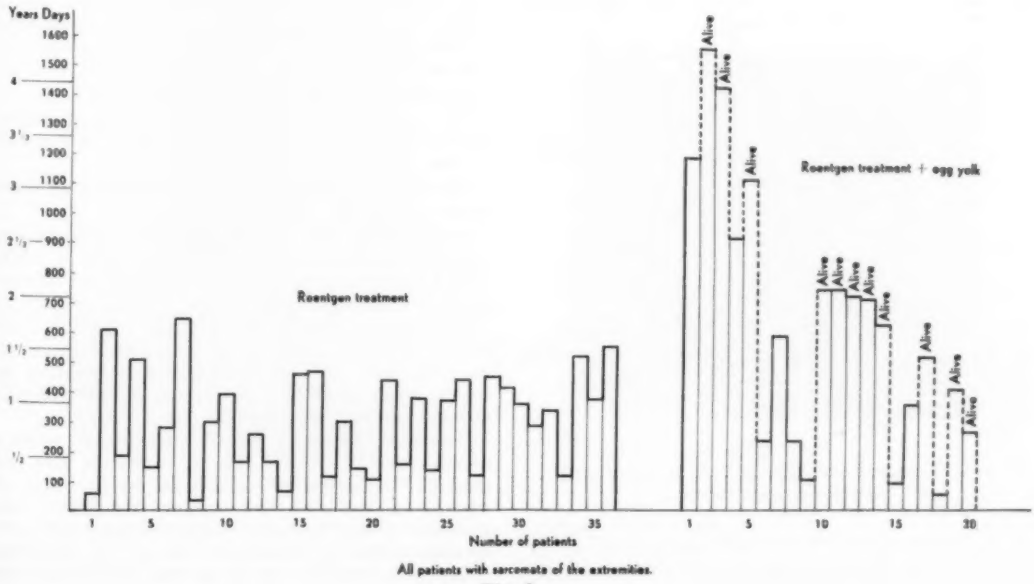

Fig. 3.

is unquestionably longer, and it is seen that half of the patients who received roentgen therapy and raw egg yolk are still alive. Similar diagrams may be constructed, both for the patients with sarcomata of the extremities over 18 years of age, and if the patients under 18 years are divided into two groups, viz. (1) osteogenic sarcomata (fig. 4) and (2) Ewing's sarcomata (fig. 5). Although the number of patients here is actually too small for graphical methods, figure 5 is yet a further pointer, as all the patients with Ewing's sarcomata who were given combined treatment are still alive.

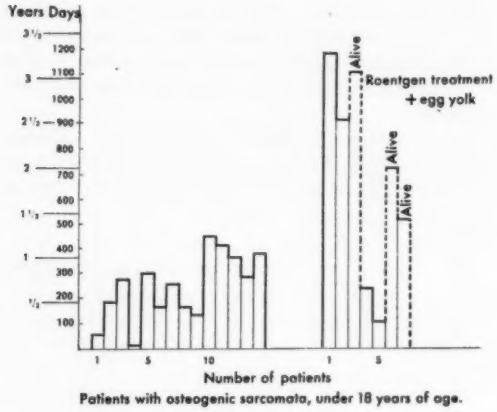

Fig. 4.

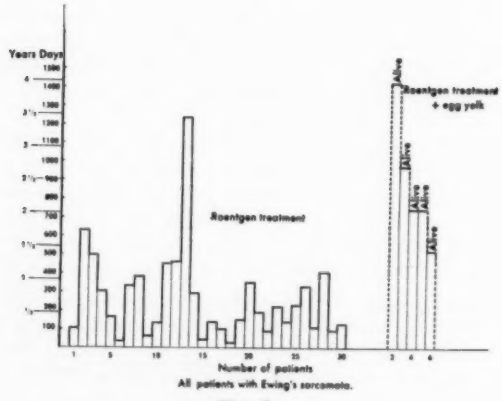

Fig. 5.

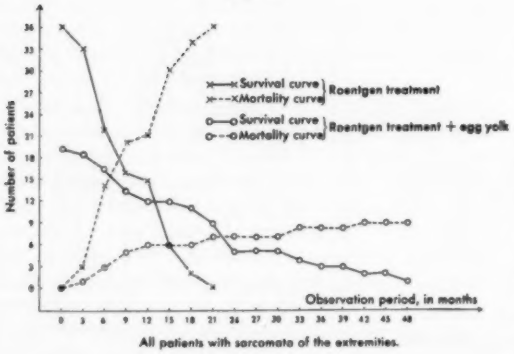

Fig. 6.

Finally, survival and mortality curves have been constructed for all the patients with osteosarcomata of the extremities (fig. 6).

The patients included in this report were given roentgen treatment every day to the extent they were able to tolerate it. Generally, a daily dose of 115 r in the morning and 115 r in the afternoon was given alternately to 4 fields. The irradiation was given at a distance of 50 cm through a Thoræus filter with a HVL of 1.4 mm Cu; the voltage was approx. 170 kV and the intensity 5 r per minute.

The yolk of 6—8 eggs was administered daily during the hospital stay; after discharge, the patients were normally given the yolk of two eggs daily for variable periods, depending on tolerance, the development of excessive obesity, etc.

When, on discharge, continued treatment with raw egg yolk at home was prescribed, the eggs were invariably sent direct to the patients through the Radium Centre.

I shall now report some illustrative cases, showing the results obtained by this combined treatment with roentgen rays and raw egg yolk.

Case 1. — A girl (750/50), aged 11, born July 21, 1938, daughter of a farmer. The patient was admitted to the Radium Centre, Århus, on March 1, 1950, with an osteogenic sarcoma in the lower end of the left femur.

Pathologist's report. — The excised tissue showed a fairly hypercellular tumour tissue. It was finely fibrillar, and the cells varied in shape from spindles to more starlike formations, with marked polymorphism. Formations of varying size suggestive of bony trabeculae with homogenization of the ground substance were frequently seen, and in these areas it often seemed as if the cells were encapsulated. The tumour must be supposed to be an osteogenic sarcoma.

Histological diagnosis: osteogenic sarcoma.

The patient had previously been in good health, but 4 months prior to admission she began to complain of pain in the left knee.

Clinically, histologically and radiologically an osteogenic sarcoma was diagnosed.

From March 7 to May 11, 1950 (i. e. 63 days), the patient was given roentgen treatment to 4 fields, 2,415 r to each (total dose 9,660 r) through a Thoræus filter at a distance of 50 cm.

The first roentgen examination on March 16, 1950, showed the usual picture of an osteogenic sarcoma with irregular densities, destruction penetrating the cortex, irregular periosteal deposits, very considerable atrophy and soft-part swelling (fig. 7).

When the patient had been treated for about a month (March 7—April 15), the condition had progressed. The destructive process in the bone had increased in size and the tumour had grown both posteriorly and laterally. Simultaneously, the sedimentation rate had increased from 6 to 16 mm/hour.

Egg yolk was then given for the first time, 6 egg yolks daily, later increased to 8.

Fig. 7.

Fig. 8.

On May 4, 1950, the picture was unchanged as compared with that from April 15, when the egg treatment was commenced. The tumour had not increased in size, but after the lapse of another month very considerable calcium deposits were noticed (fig. 8). It looked as if the marrow cavity had been filled with a »bone plug«; all tumour tissue had calcified, and the cortex had become smooth.

Fig. 9.
At institution of treatment.

On May 6, 1950, two months after the institution of treatment, the patient felt perfectly well. She was able to walk about freely and was completely well for the next 2 years. The leg looked fine, and the patient walked with only a slight limp. In spite of a long distance, the girl managed to walk to school in all sorts of weather.

However, a check-up examination on Dec. 7, 1951, i. e. 21 months after the onset of the disease, a small, rounded spot was disclosed in the upper lobe of the left lung. It measured about 4 mm in diameter, and the lateral half was calcified. A course of roentgen treatment to the lung, combined with egg yolk, was instituted. Two months later the calcification of the metastasis had become complete, but at an examination on Aug. 22, 1952, i. e. 28 months after the commencement of treatment, a fresh metastasis was disclosed. Roentgen irradiation to the upper part of the lung, combined with egg yolk, was given, and no more metastases developed in the lung.

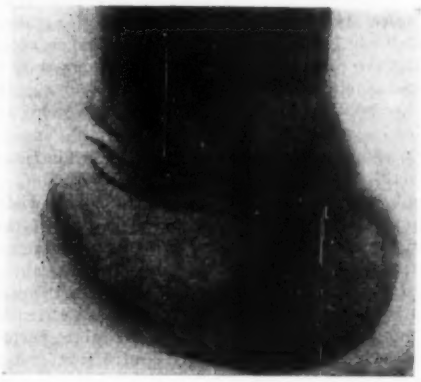

Fig. 10.
Two years later. The calcified tumour is clear of the epiphyseal line.

A total dose of 12,000 r to the femur and 10,000 r to the lungs was given.

A check-up examination 2½ years after the institution of treatment revealed that the tumour had broken through the smooth contour — the disease had recurred.

The patient was alive 3 years and 3 months after the commencement of treatment and had been given 2,760 eggs.

A comparison of the roentgenograms of the left femur shows that apparent healing had occurred 2 years after the onset of the disease (figs. 9 and 10). The tumour had become well-defined proximally and distally. The bone showed normal growth between the epiphyseal line and the tumour, and it had become perfectly smooth, but then, after the lapse of 30 months, all that had previously been gained was again lost. However, I think it may be permissible to say that the observations were beyond what is usually seen.

If this case teaches us a lesson, it is that such a patient should be kept at rest for at least two years. Such a period would give a possibility of a much better encapsulation of the tumour tissue.

Another thing which I believe is of importance is that a maintenance dose of egg yolk is given. The first metastasis in the lung developed after a period during which no egg yolk was given.

Case 2. — A girl (2444/50), aged 8, born October 16, 1941, daughter of a small-holder. The patient had been in good health until two months before admission, when she began to drag her left leg, and on July 18, 1950, the patient was admitted to the Radium Centre for a sarcoma in the upper end of the left tibia.

Pathologist's report. — In the tissue submitted some small bony trabeculae were seen, interspaced with a marrow which was mainly fibrous, but in a few areas of the marrow and in a slightly larger, loose tissue fragment there was a very hypercellular tissue, made up of fairly small cells varying in form from rounded to slightly spindle-shaped, with round or oval nuclei containing varying amounts of chromatin. Mitoses were occasionally seen in these cells, embedded in a delicate network of fine threads. In some areas vessels were present, around which tumour cells were arranged slightly concentrically. The tissue examined must be from a sarcoma, presumably a Ewing's sarcoma.

Histological diagnosis: sarcoma of the tibia (Ewing's sarcoma?).

Roentgenograms taken on July 12, 1950, showed that the upper part of the tibia down to about 8 cm below the epiphysis was the site of changes characteristic of an osteogenic sarcoma, with destruction and perforated cortex. The destruction extended throughout the entire thickness of the bone (fig. 12). A characteristic Codman's reactive triangle, irregular periosteal formation of new bone, a small infraction and soft-part swelling were seen.

From Aug. 9 to Sep. 16, 1950, i. e. 35 days, a total dose of 8,100 r was given to four fields.

The roentgen treatment was supplemented with administration of the raw yolk of 6 eggs daily, which was swollowed without discomfort.

A roentgen examination 6 weeks later (Aug. 29, 1950) showed further progression of the tumour and

Fig. 11.
Two years after institution of treatment.

of the destruction along the anterior and medial margins of the metaphysis (fig. 13), but as early as 6 months after the combined roentgen and egg-yolk therapy considerable consolidation of bone was noted (fig. 14). The patient was well for 3½ years. Then a small

Fig. 12.

Fig. 13.

periosteal reaction on the tibia developed. Treatment with roentgen rays and raw egg yolk was resumed, and after a short period deposition of calcium was observed in the tumour area.

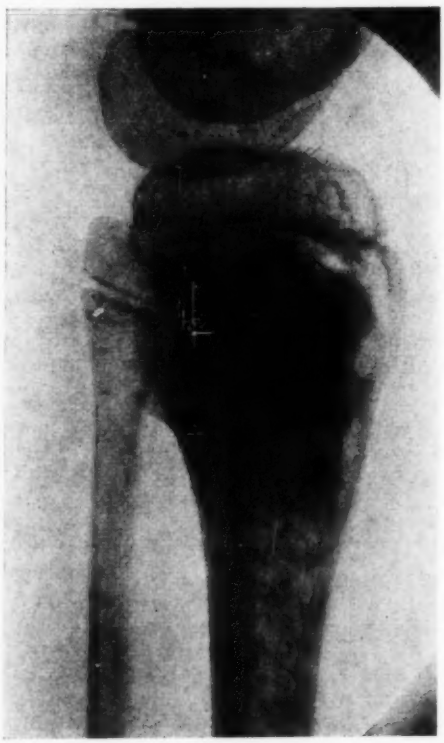

Fig. 14.

In this case, in which almost 4 years have now elapsed without the development of metastases, it might, perhaps, be wise to perform an amputation. It is difficult to make a decision in such a case. Possibly, the organism has now become "vaccinated" against metastasis formation. In this connexion I think of a study by Poppe (6), which appeared some years ago, and in which it was shown that cases of long duration gave the best results following amputation.

I believe that the results so far obtained in these two patients are better than any previously seen in the treatment of osteosarcomata.

In the next two cases reported below calcification occurred to an extent which I do not believe to have seen before.

Case 3. — A girl (3867/50), aged 15, born May 23, 1934, daughter of a small-holder. The patient was admitted to the Radium Centre on November 3, 1950, for a sarcoma in the lower end of the left femur.

Pathologist's report. — The tissue sample revealed tumour tissue which had infiltrated the striated musculature. The tissue was fairly rich in cells and showed a ground substance varying from finely fibrillar to cartilaginoid, homogenous. It contained closely packed cells showing a transition from atypical, spindle-shaped to immature cartilage cells. Scattered in the tissue, particularly in the basal part, there were some small osteoid trabeculae consisting of fibrillar or partially homogeneous tissue, in which calcium deposits and small, atypical osteocytes were present. In some places, these trabeculae vanished into threadlike processes in the surrounding tissue. The case is presumably one of sarcoma, osteochondrosarcoma.

Histological diagnosis: osteochondrosarcoma.

The patient had been in good health until 2½ months before admission, when pain in the left knee and the lower half of the left thigh developed.

On admission, diffuse swelling of the lower half of the left thigh was noted, accompanied by muscular atrophy, measuring 4 cm. above the swelling.

The roentgenograms were characteristic of an osteosarcoma, showing extensive destruction, slight spicule formation, large soft-part swelling and irregular densities and rarefactions in the bone. A total roentgen dose of 10,600 r was given to four fields through a Thoræus filter at a distance of 50 cm. The course extended over 100 days, a dose of 115 r being given to two fields each day.

During and after the course of roentgen treatment the yolk of 8, and later, 10 eggs was given daily.

The patient was well for a long period, and as I have also often seen before when the treatment was not supplemented with raw egg yolk, a satisfactory periosteal reaction occurred, but this was followed by what I believe was a new thing in my experience, viz. calcification of the lymph nodes along the femur (fig. 15).

These calcified nodes contained tumour tissue completely surrounded by a shell of calcium.

Amputation was deemed necessary. An enormous degree of calcification occurred in the amputation stump. The patient died 2½ years after the first admission. Autopsy revealed small, stone-hard metastases to the lung.

Fig. 15.

Case 4. — A girl (557/52), aged 15, born July 22, 1936, foster-daughter of a tram-conductor, was admitted to the Radium Centre on February 15, 1952.

The patient had previously been in good health.

Possibly following a slight trauma, intense pain in the knee and swelling of the region above the knee had developed 4 months before admission.

The patient had first been treated at home with bandage and hot compresses. Later, the lesion had been interpreted as tuberculosis of the knee and was treated in a sanatorium.

After the lapse of 4 months a pathological fracture occurred; a biopsy was performed, and the patient was transferred to the Radium Centre.

Pathologist's report. — The sample submitted showed a completely necrotic tissue, but some areas showed a finely fibrillar, oedematous connective tissue, while other areas showed a very hypercellular tissue with small, slightly spindle-shaped cells. These cells seemed somewhat atypical, but did not show polymorphism. The tissue was also poorly vascularized. No giant cells could be demonstrated. These very tiny areas of tissue were difficult to evaluate. The cells were markedly degenerated, and a definite diagnosis could not be made, but although it was impossible to classify the tissue, I suspect it of being a tumour tissue — a sarcoma.

During the entire hospital stay the patient had fever, dyspnoea and a rapid pulse, and after the lapse of a few months she was discharged at the request of the parents, who lived in Germany.

While in hospital, the patient was given intense combined roentgen and egg-yolk therapy (10,000 r to the femur and 360 eggs), supplemented with energetic antipyretic treatment and supportive therapy, including numerous blood transfusions.

After some time large pulmonary metastases and exudate were noticed, and the patient was discharged 2½ months after admission. Death ensued 3 weeks later.

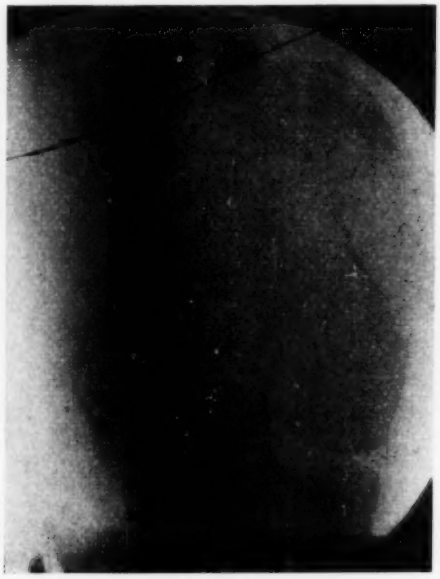

Fig. 16.

A comparison of the roentgenograms (figs. 16 and 17) shows that in spite of everything an enormous healing process had been in progress during six weeks, but it was impossible to combat the generalized disease.

When a fracture occurs in a bone which is the site of a sarcoma, treatment becomes extremely difficult. It complicates irradiation therapy, and in association with the fracture an enormous dissemination of tumour tissue may occur.

Fig. 17.

The next case is an example of complete cure in a patient with a Ewing's sarcoma of the left fibula (fig. 18).

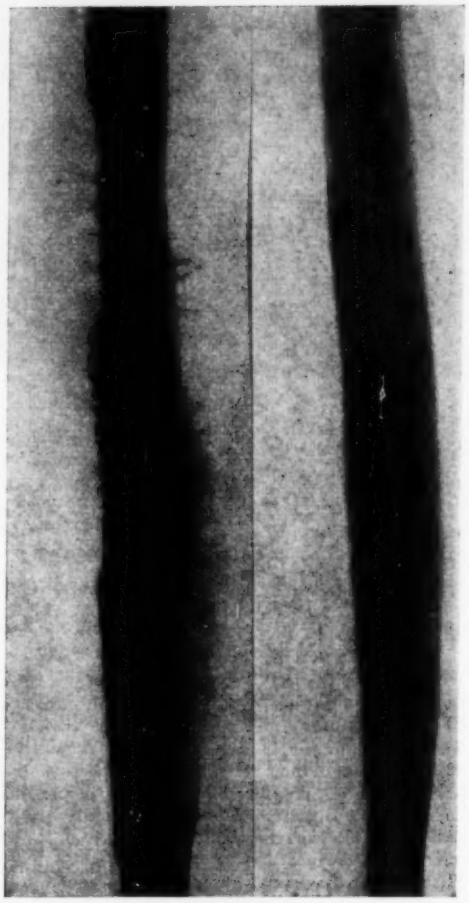

Fig. 18.

Case 5. — A girl (1992/51), aged 13, born July 29, 1937, daughter of an unskilled worker, was admitted to the Radium Centre on June 5, 1951. The patient had been in good health until 6 months before admission when she noticed a swelling on the left leg. On admission, physical examination revealed a young girl, apparently in good health. Except for the changes in the left leg, no pathological findings were disclosed. The middle third of the left leg was tender and slightly swollen; normal temperature.

Several biopsy samples were secured from the tumour, but for some unknown reason the histological examination failed, so that no histological diagnosis was made in this case.

On the other hand, the roentgenograms seemed to be almost classic, with spicule formation, destruction of the cortex, Codman's reactive triangle and soft-part swelling.

The patient was given roentgen treatment to four fields, 7,800 r in the course of 6 weeks, and the raw yolk of 8 eggs daily for 5 months.

A comparison of the roentgenograms showed that the process was rapidly smoothed out; the spicule formation disappeared, and at the time of writing, 38 months later, it is impossible to see that there has ever been a pathological process in the leg. The patient seems to be fully recovered.

Fig. 19.

In view of the local results obtained and the absence of a histological diagnosis, this case should, perhaps, have been excluded from the report, but the radiological appearance was classic; 5 months after the treatment a small shadow, which was undoubtedly a metastasis, appeared in the lung to the right of the heart border. During the following period the shadow increased in size, and two years after admission a definite metastasis was diagnosed (fig. 19). During the

Fig. 20.

entire period, the patient had been given the raw yolk of two eggs daily to check the growth of the metastasis, but suddenly it seemed as if the resistance of the organism had been broken, and the metastasis rapidly increased in size. Roentgen irradiation was therefore given to the metastasis, supplemented by the raw yolk of 8 eggs daily. The metastasis began to subside. At the time of writing, 3 years after the institution of treatment, it has completely disappeared (fig. 20), and the patient is apparently fully recovered.

Fig. 21.

Case 6. — A girl (1716/52), aged 16, born July 23, 1936, daughter of a draper, was admitted on June 11, 1952. From early February 1952, the patient had had pain in the right leg, just below the knee, at first dull and intermittent, later increasing in intensity. Roentgenograms then showed a destructive process in the upper 8 cm of the right fibula with a large number of spicules radiating into a large soft-part tumour, which laterally extended 1.5 cm outside the substantia compacta, medially a little less (fig. 21).

Roentgenologically, it was undoubtedly a sarcoma of the upper end of the fibula. On the other hand, the histological examination of tissue samples gave rise to some doubt as to the proper diagnosis; the preparations were submitted to several competent pathologists (Vimtrup, Engelbreth-Holm, Schourup and Teilum), who agreed that it was a case of Ewing's sarcoma.

The patient was treated with roentgen irradiation and raw egg yolk and is now, more than 2 years after the admission, fully recovered (fig. 22).

Case 7. — A bank clerk (3094/52), aged 21, was admitted on October 8, 1952, with a sarcoma of the metatarsus, which showed an enormous tendency to rapid healing after combined therapy.

Fig. 22.

Pathologist's report. — Sections showed a highly cellular tumour tissue, which in certain areas was also fairly vascular. Interspaced with fine vessels, the tissue was arranged in bands or bundles with fine threads and numerous cells. The cells were spindle-shaped, slightly polymorphic with hyperchromatic nuclei, and the fibrils were only occasionally differentiated into collagen threads. The growth of the tumour was ill-defined.

Histological diagnosis: spindle-cell sarcoma.

Complete regeneration of the bone occurred after

Fig. 23.

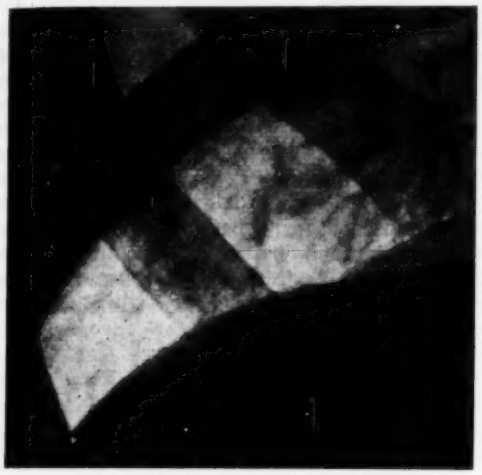

Fig. 24.

combined treatment with roentgen irradiation and raw egg yolk.

Six months later metastases to the lungs developed (fig. 23). Combined therapy was resumed, and at the time of writing, 21 months after the initiation of treatment, the patient is apparently fully recovered (fig. 24).

Case 8. — A boy (1884/52), aged 8 years, was admitted on June 26, 1952, with an osteogenic sarcoma of the upper end of the tibia (fig. 25).

Pathologist's report. — The excised tissue showed a fairly cellular tumour of osteoid structure. It consisted of finely fibrillar, cellular tissue, which in many areas revealed the formation of osteoid anastomotic, relatively narrow trabeculae and branches of dense, fibrillar and, often, somewhat homogenized tissue with deposits of calcium. Between these trabeculae the tissue was finely fibrillar, with spindle-shaped cells of variable size, and there were also some scattered giant cells of osteoclastic type. Adjacent to the bony trabeculae, some fairly large, osteoblast-like cells, rich in protoplasm, were observed. The tissue is highly suspect of being from the margin of an osteosarcoma.

Fig. 25.

Four months before admission the patient had been kicked by a horse. Destruction of bone, with soft-part swelling and spicule formation, was seen in the upper part of the tibia; from just below the epiphyseal line it extended downwards and laterally. Two courses of roentgen therapy were given, totalling 7,935 + 5,750 r, supplemented with the raw yolk of 6 eggs; after discharge, the patient was given two eggs daily. At the present time, more than 2 years after the institution of treatment, the patient is alive and well (fig. 26). No metastases have developed, but there is a slight valgus position of the left knee.

Fig. 26.

I have reported some illustrative examples of patients with osteogenic sarcomata, who were treated with roentgen irradiation in combination with raw egg yolk. It may be said that the effect which was observed in children was also reflected in adult patients, although it was much less conspicuous. The present paper must be regarded as a preliminary report. At the present time it is not possible to say whether the method can effect a cure in such patients, but I believe that raw egg yolk may be utilized in supporting the fight of the organism against osteosarcoma. Ultimately, it may be possible to isolate substances with a curative effect from the eggs and concentrate these substances, so that a more potent remedy is obtained.

SUMMARY

All investigators who have studied osteosarcomata will have observed that these tumours, generally starting in the metaphysis or diaphysis, are nearly always arrested by the epiphyseal line,

only in rare cases growing through it and then only after the lapse of a prolonged period of time.

I have studied this problem for many years in order, if possible, to find therapeutic means capable of arresting the growth of these tumours.

I attempted if the raw yolk of 6—8 eggs given as a supplement to the roentgen therapy should have any beneficial effect, as it must be supposed that raw, fresh egg yolk contains the requisite growth hormones. In order, if possible, to increase the tendency to deposition of calcium in the tumours — a tendency which must surely be considered an important factor in the healing process —, the hens laying the eggs used for this purpose were fed a diet containing common mussels.

None of the 31 patients who were treated during the 14-year period (1937—1950) before this combined roentgen and egg-yolk therapy was introduced, are alive, although the treatment was carried out with the greatest zeal and care. The average duration of survival for these patients was 250 days, whereas that for the seven patients reported on in a previous paper is now 811 days.

A number of illustrative cases are reported, in which the results of combined roentgen and egg-yolk therapy are shown. Judging from these results, it can scarcely be doubted that raw egg yolk given as a supplement to roentgen therapy has a beneficial effect in children. Healing to an extent which I believe never to have seen before was obtained; the calcification reached a degree which was far more pronounced than that obtained before the introduction of the combined therapy, and the duration of survival was considerably prolonged. Several of the children treated with roentgen irradiation and raw egg yolk were well for years, but then the disease suddenly recurred. Metastases to the lungs seem also to be subdued by the combined therapy to a degree which was never observed before its introduction. It is more problematic if it is possible to obtain a good result in the treatment of osteosarcomata in adults by this method, but it seems to give a certain effect and a longer period of survival.

ACKNOWLEDGMENT

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HEXAMETHONIUM TREATMENT OF ARTERIAL HYPERTENSION

By VAGN RØNNOV-JESSEN

Hexamethonium preparations have now been employed for nearly 5 years in the treatment of hypertension. During the first years, particularly, very diverging views were held concerning the applicability of the drug. Some investigators found it quite unsuitable and could only demonstrate a transient effect on the blood pressure (Locket et al. 1951 and Blainey 1952) while others observed good effect not only on the blood pressure but also on the subjective and objective symptoms (Restall & Smirk 1950, Smirk & Alstad 1951, Morrison 1953). The investigators who obtained the best results, employed practically exclusively subcutaneous administration which produces a fairly constant effect from day to day, while when oral administration is employed, a very varying effect on the blood pressure is achieved and more side-effects are encountered. Kilpatrick & Smirk (1952) state that only in approximately 25 per cent. of the cases were satisfactory results obtained by oral administration alone. In Denmark, Bechgaard, Iversen & Levin Nielsen (1951) found that oral administration was only practicable in a minority of cases. In the majority, the inconveniencies were so great that the patients did not desire continued treatment.

In recent years, particularly in U. S. A., there has been a tendency to combine oral treatment with hexamethonium with oral administration of l-hydrazinophthalazine (Apresolin) and the results obtained are promising (Freis et al. 1952, Johnson et al. 1952, Schroeder et al. 1953, Morrow et al. 1953).

From the Department of Medicine, the County Central Hospital, Frederiksborg, Hillerød. Physician-in-Charge: *Torben Andersen,* M. D.

Smirk (1954) recently reported on his results of treatment with methonium for 3½ years. He treated a total of 250 patients. The large majority received hexamethonium and only a minority received other methonium compounds. 28 patients suffered from malignant hypertension with papilloedema. 21 out of these patients are alive with an average period of survival of 22.8 months, while 7 have died after an average of 9.7 months treatment and Smirk regards this as a significant improvement of the prognosis. In patients with fundus hypertonicus II and III he found a somewhat lesser mortality than in a control group but he did not venture to express the opinion that this implies a definite alteration of the prognosis.

AUTHOR's INVESTIGATIONS

Method and Dosage.

The treatment was initiated when the patients had been hospitalized for 8—14 days in the department. In this way, the blood pressure had time to become stabilized and patients in whom the blood pressure fell spontaneously could be sifted out. The patients were up and about during the entire period of hospitalization apart from the first 3—5 days. During the entire stay in hospital, the blood pressure was measured thrice daily in the upright position.

Combined subcutaneous and oral treatment was used. In the majority of cases, 10 per cent. hexamethonium in aqueous solution was employed as the injection fluid at the commencement. Later, in nearly all cases, 20 per cent. hexamethonium bromide in an aqueous solution of 25 per cent. polyvinyl pyrrolidone (Vegolysen Retard*)) was employed. Orally, hexamethonium bitartrate in tablets of 350 mg. (Vegolysen tartrate) was administered. The principles of treatment were described in detail in previous works (Rønnov-Jessen & Bech 1953 and Rønnov-Jessen 1953 a) and will only be briefly mentioned here.

The patients received 2 subcutaneous injections daily, as a rule at 7 a. m. and 2 p. m. The initial dose was 15—20 mg. hexamethonium bromide. The dose was increased according to the development of tolerance and in isolated cases, the single dosage had to be increased to more than 200 mg. Before lunch and supper and at bed time, the patients received 350—2,450 mg. hexamethonium bitartrate dissolved in water orally.

When the first period of adjustment was over and the patients had learned to administer the injections themselves, they were discharged home. This occurred, as a rule, after 10—20 days of treatment. In the majority of cases, maximal tolerance is not obtained until after treatment for several months and therefore the patients were admitted in the earlier stage approximately once a month for a couple of days in order to correct the dose. After 3—4 months the control examinations were reduced so that the patient then appeared every third to sixth month only.

Prior to discharge, the patients were thoroughly instructed how best to counteract the orthostatic vertigo: in slighter cases by moving about calmly and in more pronounced cases by lying down. Should they think they were receiving an overdosage they were to report to the department for correction of the dosage. Should the treatment be discontinued for some days for one reason or another, it should not be recommenced without consulting the department, because the acquired tolerance diminishes rapidly so that recommencement of the treatment with unchanged dose may cause distinct overdosing.

Results.

To date, 28 patients have been treated (18 females and 10 males) according to these principles. At the commencement of the treatment the patients were aged 35—70 years, the average being 52 years. All patients suffered from severe hypertension with high diastolic blood pressure and according to Hammerström & Bechgaard's criteria (1950), 9 patients may be classified in Group IV, 18 in Group III and only 1 in Group II.

Three patients discontinued treatment within 3 months on account of failure to improve and one died after 6 months from uraemia after an attack of pulmonary oedema. The remaining 24 patients have been treated for 12—34 months; on an average for 16 months.

Effect on Blood Pressure. During treatment, distinct reduction of the blood pressure in the upright position occurred in all cases and in those patients in whom it was measured, reduction of the blood pressure in the supine position was similarly observed.

The control blood pressure was determined as the average of the blood pressure measurements during the last 2 days prior to the commencement of treatment. The blood pressure during treatment was measured on the last control admission and calculated as the average of 3 measurements, approximately one hour and 6 hours after the first injection and 5—6 hours after the second injection. In the upright position, the reduction of blood pressure was, on an average, 55/35 mg. Hg. and approximately 4/5 of the patients showed lowering of blood pressure exceeding 40/20 mm. Hg. In those patients in whom the blood pressure was also measured in the supine position, the reduction was, on an average, 40/30 mm. Hg.

Effect on Subjective Symptoms. The effect has only been analysed in those patients who have been treated for more than 3 months.

Prior to treatment, 16 patients were disturbed by dyspnoea on exertion, which has now dis-

*) Messrs May & Baker Ltd. supplied the hexamethonium compounds.

appeared or diminished in 15. Approximately 3/4 of the patients complained previously of headache. The majority are now completely free from this complaint and only in one the headache persists unchanged. Slightly more than half of the patients suffered from vertigo which has either disappeared or diminished significantly. A number of the patients, however, suffer now and again from transient vertigo of hypotensive origin. Several suffered from angina pectoris prior to treatment and in all of those the attacks have become less frequent. In one patient, who had not previously suffered from cardiac pain, stenocardiac attacks appeared during treatment.

Subjective Condition and Capacity for Work. More than 4/5 of the patients state that during treatment an improvement of their general condition occurred and nearly half of the patients with the pronounced and most severe symptoms have become practically symptomfree during treatment (see Table I).

Table I.
Subjective Condition Prior to and During Treatment With Hexamethonium.

Prior to Treatment	During Treatment: Practically Symptom-free	Improved	Unchanged	Deteriorated
Slight Inconvenience ..	3	2	1	
Pronounced » ..	18	9	6	2[2]) 1[2])
Most Severe » ..	7	3	3[1])	1[2])

[1]) One patient died from pulmonary oedema and uraemia after 6 months treatment.
[2]) Treatment discontinued in 3 cases.

The effect on the capacity for work which appears from Table II is of great social significance. In 20 of the patients, the capacity for work was considerably reduced; in 12, it has improved during treatment while 6 patients have become completely fit for work.

Table II.
Capacity for Work Prior to and During Treatment With Hexamethonium. The 3 Patients Who Discontinued Treatment During the Course of the First Months are Not Included.

Prior to Treatment	During Treatment: Completely Fit for Work	Improved	Unchanged
Completely Fit for Work 5	5		(5)
Partially » » 11	5	2	4
Unfit for Work 9	1	4	4[1])

[1]) One patient died from pulmonary oedema and uraemia after 6 months treatment.

Changes in the Objective Findings. Nearly all the patients showed pathological electrocardiograms prior to treatment. In 11 patients, regression of the electrocardiographic changes took place. Negative T-waves became flatter or positive, iso-electric or flat T-waves became higher, and negative S-T-intervals became iso-electric. During treatment, one patient developed a transient bundle-branch block. Definite reduction of the left-sided axis deviation was not observed in any case.

In one case, definite reduction in the size of the heart took place. In the other patients, the changes were not greater than the variations frequently encountered in repeated X-ray photographs of the chest of the same patient.

In 3 patients with increased blood urea, further increase occurred. One developed, in addition, pronounced hypotension which was manifested by vertigo and a tendency to faint so that for several days she could not stand up. Continued treatment was abandoned. In the other two, the blood urea, however, fell again; in one of the cases, however, this fall was only transient as the patient died from uraemia following an attack of acute pulmonary oedema after treatment for 6 months. The other patient has still slight uraemia after 16 months treatment but feels well otherwise and is completely fit for work. The remaining patients did not show increase in blood urea during treatment. In several cases, the diuresis during day time is only minimal while at night the diuresis is very copious.

All patients had hypertensive changes of the fundus of the eye prior to treatment. In several cases, haemorrhages and exudates disappeared and in 2 patients with papilloedema, this disappeared in the course of some months. (See also Table III).

Table III.
Changes in the Fundus Prior to and During Treatment With Hexamethonium.

Degree	Prior to Treatment	During Treatment I	II	III	IV	Treatment Discontinued
I	2	2				
II	15	14				1[2])
III	9	4		3[1])		2[2])
IV	2	1		1		
Total	28	21		4		3

[1]) One patient died from pulmonary oedema and uraemia after 6 months treatment.
[2]) Treatment discontinued within 3 months.

Side-Effects.

During the first months of treatment, the side-effects were frequently very troublesome but during continued treatment they diminished in several cases. At the time of writing, 4/5 of the patients suffer from constipation which, however, is well regulated in nearly all. Half of the pa-

tients require only paraffin emulsion and linseed while the remainder, in addition, receive 15—30 mg. Neostigmine orally in the morning.

In 3 patients, transient episodes of diarrhoea occurred during treatment which, however, disappeared on reduction of the dose of hexamethonium for some days.

A number of patients have occasionally been inconvenienced by vertigo of hypotensive origin, as a rule approximately one hour after the injection.

Isolated patients complained of giddiness and blackness before the eyes on exertion and in a couple of cases, there was, in addition, a feeling of oppression in the chest and of heaviness in the arms. Exercise tests with Krogh's cycleergometer showed that these symptoms were due to fall in blood pressure on exertion. The fall in blood pressure was most pronounced when the blood pressure was low prior to the commencement of exertion and the symptoms decreased or disappeared completely on reduction of the dose of hexamethonium (Rønnov-Jessen 1953 b and c).

Isolated patients complained of blurred vision and some of dryness of the mouth and throat. Three patients (all female) complained of symptoms associated with micturition; two of them had difficulty in emptying the bladder when the effect of hexamethonium was marked while the third suffered from vesical tenesmus. These symptoms diminished in all during continued treatment. Two patients developed transient incontinence of urine on acute overdosage of the drug. Six patients felt more tired than previously, particularly at the commencement of the treatment, and 2 complained of reduction of the sense of taste.

No actual complications of the treatment were seen. One patient developed a slight hemiparesis while cleaning in the morning. The paralysis developed before she had taken her morning injection, i. e. at a period when the blood pressure was undoubtedly high. None of the remaining patients developed cerebral haemorrhages nor thrombosis in the brain or heart.

DISCUSSION

Treatment with hexamethonium is complicated and the side-effects are frequently considerable for which reason this form of treatment is only suitable for a limited number of patients suffering from hypertension.

All patients in the present series suffered from severe fixed hypertension. The author treated preferably such patients who had, in addition, considerable subjective symptoms, as the subjective improvement in these patients is, as a rule, so marked that it more than compensates the inconveniences so that the patients themselves are interested in persevering with the treatment. Patients with slight subjective symptoms were treated by the author only if the blood pressure was very high as prolonged treatment is difficult to carry through when the side-effects of the treatment are more troublesome than the disease.

Prolonged treatment can only be carried through in patients with normal intelligence and ability to co-operate.

The principal contraindications are recent thromboses in the brain and heart. Patients with signs of severe arteriosclerosis were not treated by the author. On the other hand, the author set no upper age limit but was guided primarily by the »physiological age« of the patients.

CONCLUSIONS

Hexamethonium is an effective preparation to produce lowering of the blood pressure, which when employed in suitable cases of hypertension, may render both subjective and objective improvement.

The treatment is complicated as, inter al., the drug must be administered subcutaneously or subcutaneously and orally in the majority of cases. Pronounced side-effects are frequently observed. The patients must, therefore, be carefully selected and treatment instituted only when considerable hypertension and pronounced subjective symptoms are present.

The effect of treatment with hexamethonium on the prognosis of hypertensive disease is not yet elucidated and possibly will never be so because new and apparently superior preparations are now available for oral therapy.

SUMMARY

Twenty-four patients with severe fixed hypertension were treated with hexamethonium for 12—34 months; on an average for 16 months. Four additional patients commenced treatment and of these treatment was discontinued in three within 3 months on account of failure to improve while the fourth died of uraemia following treatment for 6 months. In all cases, treatment was combined subcutaneous and oral.

In all patients, reduction of the blood pressure occurred, particularly in the upright position, of on an average 55/35 mm. Hg. In the majority of cases, improvement of the subjective symptoms of hypertension took place. In a number of patients, reduction of the objective symptoms also occurred: papilloedema, haemorrhages and exudates disappeared from the fundus of the eye and the electrocardiographic changes regressed.

The side-effects were noh uncommonly troublesome. The most important, viz. orthostatic vertigo, misty vision and fatigue, frequently diminished during continued treatment.

The author concludes that hexamethonium is an effective agent in lowering the blood pressure, which may render both subjective and objective improvement in suitable cases. As the treatment

is rather complicated, and the side-effects quite considerable, the patients should be selected with care and treatment only instituted if considerable hypertension and pronounced subjective symptoms are present.

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NOSOCOMIAL INFECTIONS WITH KLEBSIELLA IN LESIONS OF THE URINARY TRACT

By IDA ØRSKOV

In 1949 Kauffmann (7) set up 14 Klebsiella capsule types in such a way that this system now includes certain capsulated bacteria previously described by various authors as Friedländer's bacillus, B. rhinoscleromatis, ozaena bacillus, Aerobacter aerogenes or Bact. lactis aerogenes. The first six types were known already but designated by other names; the latter eight were established as new capsule types. Among 100 urinary strains 20 were found to belong to type 8, 40 to type 9, and 33 to type 10.

In 1951 Brooke (1) found 27 new capsule types and on examination of 265 urinary strains he confirmed that types 8, 9 and 10 made up a large percentage of these strains. Of the remaining 30 types isolated by Brooke from specimens of urine, relatively many strains belonged to types 7, 24, 31 and 38.

Furthermore, Worfel and Ferguson (10) have described one new type and Edwards and Fife (3) isolated 18 capsule types in addition. They write "the marked predominance of types 8, 9 and 10 noted by Brooke and Kauffmann was not evident in this study." They examined 85 urinary strains but found no predominance of any special type. They do not state from how many different wards they have received the specimens.

In Kauffmann's materiel as well as in that of Brooke the strains were isolated from specimens of urine received by Statens Seruminstitut for bacteriological sensitivity determination. From neither of the two investigations is it evident from which hospitals the specimens originated nor how the types were distributed on male and female patients.

During my daily work in the Bacterial Resistance Department of the institute it occured to me that it might prove worth while to look into these aspects of the types, as there was a striking uniformity of sensitivity among Klebsiella strains isolated from patients in the same hospital.

MATERIAL AND METHODS

In this study altogether 388 capsulated Klebsiella strains were investigated, collected from 322 patients. The examination of these specimens of urine covers a period of about 18 months. From some of the hospitals, however, the specimens were not received regularly. Furthermore it is to be mentioned that no selection of the strains has taken place, it was only required that the strains fermentatively must be typical Klebsiella strains, with no regard being paid to their sensitivity.

The determination of the sensitivity to penicillin, sulfathiazole and streptomycin has been carried out according to the tablet method (8); the zone of inhibition is recorded in mm. It is to be mentioned that all the strains in vitro have proved sensitive to aureomycin, chloromycetin and terramycin, for which reason their aspects of sensitivity to these substances are not recorded.

Serologically all strains have been identified as to their capsule antigen by means of the at that time existing 54 sera. It proved here practicable to type 384 of the strains.

From Statens Seruminstitut, Copenhagen.
Director: *J. Ørskov.*

Table 1.
Typedistribution of Klebsiella strains on surgical male wards in Copenhagen.

Hospital	Predominant capsule type	Number of ptt. with predom. type	Total number of ptt. with Klebs.	%	Resistance *p.	sulf.	str.	First specimen	Last specimen
A_1	8	31	41	75	0	0	0	Oct. 50	Aug. 51
A_2	—	—	7						
B	8	6	18	33	0	0	0	May 51	Oct. 51
	9	7	18	38	0	0	0	June 51	Oct. 51
	10	7	18	38	0	0	0	Nov. 50	Aug. 51
B out-pat.	—	—	3						
C	8	4	5	80	0	0	0	May 51	Sept. 51
D_1	10	6	7	85	0	0	0	Oct. 50	Sept. 51
D_2	10	5	5	100	various			May 51	March 52

RESULTS

The type distribution of Klebsiella strains from male surgical clinics in Copenhagen is evident from table 1. Hospitals in which Klebsiella strains were isolated from less than three patients are not included in the two tabulations. Only when one and the same capsulate Klebsiella type was obtained from three patients or more this number is recorded in percentage of the total number of patients from whom Klebsiella strains were isolated. Furthermore, it is not recorded in the tables to which types those Klebsiella strains belonged which were found in the different wards beyond the predominant type.

Departments A_1, A_2 (*i.e.*, two departments in the same hospital) B and C are all municipal clinics to which larger os smaller numbers of patients with affections of the urinary tract will be admitted at any time.

In Dept. A_1 from which we have received the greatest number of specimens, we find predominance of type 8. Here it may be added that this type was found in nearly 50 % of all specimens (*i.e.*, specimens of urine including those where Klebsiella was not found) received from this ward. As to Dept. A_2, no predominant type was encountered here. But it is also to be mentioned that, in contrast to this clinic, Dept. A_1 has constantly a considerable number of patients with urinary affections.

Dept. B has a fairly equal distribution of type 8, 9 and 10 (in some specimens two of these types were found at the same time). From the out-pat. Dept. we isolated three different types from three patients. In Dept. C type 8 is the predominant type.

Hospital D is situated in Copenhagen but it admits patient from Copenhagen County. In Dept. D_1, we find type 10 in six out of seven patients, in Dept. D_2 the same type in all five patients.

Table 2 shows the type distribution of Klebsiella strains in male surgical clinics outside Copenhagen. Here the type distribution has varied somewhat more from one hospital to another than was found in Copenhagen; yet we

Table 2.
Typedistribution of Klebsiella strains on surgical male wards in the country.

Hospital	Predominant capsule type	Number of ptt. with predom. type	Total number of ptt. with Klebs.	%	Resistance *p.	sulf.	str.	First specimen	Last specimen
1	8	7	9	77	0	0	0	Nov. 50	Aug. 51
2	10	6	6	100	0	0	0	April 51	Jan. 52
3	24	17	17	100	0	0	30	Dec. 50	Feb. 52
4	—	—	4						
5	24	4	5	80	0	20	0	Nov. 50	Aug. 51
6	2	3	3	100	0	0	0	July 51	March 52
7	38	17	17	100	0	0	30	Oct. 50	Jan. 52
8	—	—	3						
9	7	4	4	100	0	20	0	Oct. 50	April 51
10	7	6	6	100	0	20	0	Dec. 50	May 51
11	10	5	7	71	0	0	0	May 51	Feb. 52
12	8	16	17	94	0	0	0	March 51	Feb. 52

* p. = penicillin, sulf. = sulfathiazole, str. = streptomycin.

meet again with a distinct uniformity of the distribution within the same clinic.

Apart from hospitals 4 and 8 we find in each hospital a predominant type. Type 24 was isolated both in hospital 3 and 5 but the fermentation reactions of the strains differed from one hospital to the other and so did also the aspects of sensitivity to sulfathiazole. Type 7 is the predominant type in hospital 9, and in the central hospital, designated as 10, which receives patients from the local hospital 9, we find the same type.

The time interval for the finding of one definite type in some specimens of urine from the same patient varies from a few days to 7 months.

As to the clinical diagnosis, no direct question was asked of the hospitals. But from the diagnoses accompanying the specimens it is safe to conclude that in the greater majority of the cases from male surgical clinics the affection involved obstruction of the urinary tract, most often hypertrophy of the prostate, more infrequently concretions, cancer or urethral stricture.

The number of specimens containing Klebsiella received from male medical clinics and from female medical and surgical clinics is smaller than the number of specimens from male surgical clinics entered in the tabulations, on which account we shall not enter further into these investigations. Still, for the sake of comparison, it may be mentioned that

202	male	surg.	pats.	in	33	depts.	yielded	18	types
43	»	med.	»	»	18	»	»	19	»
38	female	surg.	»	»	20	»	»	19	»
39	»	med.	»	»	24	»	»	26	»

From this it seems justifiable to conclude that the distribution of the type on the male surgical departments is more uniform than on the other groups.

Undoubtedly the uniformity of the type distribution is due to cross infections in the clinics. In order to investigate the frequency of such infections, the point of time for its manifestation and the ways in which the patients become infected, examinations were carried out in collaboration with Dept. A_1.

From 106 catheterized male patients in this surgical clinic in Copenhagen specimens of urine were examined for the presence of Klebsiella type 8, as this type was the dominant type among urinary Klebsiella types isolated from this clinic. Specimen No. 1 from each patient was expected to be sent to the institute immediately after the first catheterization and specimen No. 2 about one week after the first one, if the patient at this time was catheterized, in reality it was taken on an average 15 days after the first one. The specimens were received from April 1952 to January 1953 and supposedly all patients who were catheterized were having their urine examined. Except in a couple of cases all patients were suffering from obstructive urinary lesions of some kind or other — most often hypertrophy of the prostate.

In 6 patients type 8 was found in the first specimen. According to the case records only in two of these 6 cases the specimen was taken at the same time as the catheter was applied, in both cases, however, the patient had previously stayed in this clinic. No second specimen of urine from these 6 patients was requested.

For various reasons specimen No. 2 from 33 patients was not received. After insertion of an indwelling catheter, some of the patients had been discharged, transferred to another clinic or had died before specimen No. 2 was taken. In other cases the catheterization was performed only once and, finally, in some cases it had been forgotten to take this specimen.

As to the remaining 67 patients type 8 was isolated from 34 of these (50 %). In all these patients more or less extensive operative intervention had been performed on the urinary tract, so an indwelling catheter in 11 cases had been used for 3—14 days before specimen No. 2 was taken. On the remaining 23 patients, besides application of catheter à demeure, cystoscopy or/and operative intervention on the urinary tract were performed together with following drainage and application of various kinds of catheters before specimen No. 2 was sent to the institute.

In order to trace the presence of type 8 in different places in the clinic 43 small lactose bromthymol blue plates were placed, with the cover removed, in various places for 24 hours. From one to three colonies of Klebsiella type 8 were obtained on 19 of the plates exposed in this way.

Cultures were likewise made from the hands of 19 of the personel, most of these nurses. Only the hands and forearms of the assistent who cleaned the urinals from a greater part of the clinic yielded growth of type 8. In some cases type 2 was obtained in cultures from clean urinals and »bed flasks« (*i.e.* flasks placed in the bed to receive the flow from the indwelling catheter).

An examination of 10 sterile catheters from 10 different tubes in which they were kept showed that these had to be regarded as sterile.

15 feces samples from 14 of the respective patients were examined for the presence of type 8, but only in one case type 8 was found.

In samples of urine sent to the Institute by general practitioners for bacteriological sensitivity determination Klebsiella strains were isolated belonging to the same types as many of the strains from the hospitals. The patients might possibly have been admitted previously to a clinic where the dominating Klebsiella type was the same as that now found in the sample of urine forwarded by the practitioners. Therefore, we wrote to 21 practitioners and asked them whether the respective patients had been hospitalized previously and, if so, in which clinic. In 6 cases

no information could be given or the patients had been admitted to clinics in which the dominant Klebsiella type was not known since urinary specimens had not been examined earlier from these clinics. In 10 of the remaining 15 cases the Klebsiella type found in the specimen of urine received from the respective practitioners may have been acquired in the clinic to which the patient had been admitted. In 7 of these 10 cases the growth was a pure culture of Klebsiella.

DISCUSSION

The literature has brought numerous reports of Klebsiella cultures isolated from cases of urinary infections. In 1949 Wilhelm & Orkin (9) demonstrated an increased pathogenicity of B. lactis aerogenes (= Klebsiella) infections. They think that this organism often is the cause of serious infections. They found a relatively greater number of resistant strains in the patients admitted than in the non-hospitalized and they explain this difference as attributable to the circumstance that at least some of the former had become infected after their admission to the hospital.

Since Kauffmann (7), Brooke (1) and Edwards (3) have reported their investigations it has become practicable to carry out an adequate analysis of the Klebsiella strains. So now with strains available from a number of different hospitals and clinics as in the present material — it turns out that in particular the male surgical clinics, so to speak are characterized by the presence of one or a few bacterial types. That the type distribution for the various clinics in Copenhagen is fairly uniform may possibly be attributable to the circumstance that here the investigation involves municipal hospitals where the same patient sometimes is admitted to one clinic sometimes to another, or has been treated off and on in various out-patient clinics. From studies of urinary Klebsiella strains in Norway, Henriksen (4) has found type 30 dominating in two clinics, a type which does not play a similar role in any hospital examined here in Denmark; so his results as to the cross infections are in good agreement with those reported here.

It is a surprising fact that one definite type may be demonstrated in a clinic as the dominant Klebsiella type through such a relatively long period. It seems reasonable to imagine that a selection is taking place of strains and types more resistant to antibiotics, drying, sunlight, etc. Furthermore there will always be some patients who are capable of "isolating" and transmitting the definite types.

These studies deal exclusively with Klebsiella strains but it seems most likely that quite corresponding features prevail in urinary infections with B. coli, Proteus and other bacteria. Recently Erlanson and Jönsson (2) have shown that this was also the case in some urinary infections with coli strains.

As to the origin of the infection it seems reasonable to conclude that in many cases it must be due to introduction of instruments into the urinary tract. When the catheter stays permanently in the urethra it will undoubtedly give rise to an ascending infection. In the clinic where some of the studies were carried out we know that Klebsiella type 8 is to be found in the air and in the bed flasks which receive the urine in which the bacteria can multiply. As to the presence of type 8 in the intestinal canal, no definite information is obtained from the studies here reported, but if the fecal material had been larger it would undoubtedly have been possible to show that in many cases the Klebsiella type concerned can be grown also from the intestinal canal, when the patients have stayed in the clinic for some length of time, and the bacteria may then be carried from the anus to the urethra round the permanent catheter.

Owing to the similarity of the bacterial growth from the intestine and from the urinary tract Hjort & Sletvold (5), Jensen (6) and others think that probably hematogenous or lymphogenous spreading of the bacteria from the gut to the urinary tract has taken place in these cases. It seems rather likely, I think, that the urinary infections sometimes may be brought about in this way; but when this affection is such a common phenomenon also after application of an indwelling catheter without any operative intervention, it seems more obvious to assume the urinary affection to be attributable to an ascending infection.

SUMMARY

The present work deals with the type distribution of Klebsiella strains isolated from specimens of urine. Altogether 388 strains have been investigated, and these strains originated from 322 patients distributed in different hospitals and clinics. From the serological determination it is shown that the type distribution, specially in the surgical male departments is very uniform. This can only be explained by nosocomial infections.

Through a period of 9 months specimens of urine from all catheterized patients in a surgical male ward were examined for the presence of Klebsiella type 8, as this type was the predominant type in this ward. It was found that 34 of 67 patients (50 %), all treated with an indwelling catheter, were infected with type 8 during the 2 weeks following the application of the catheter.

In a material of Klebsiella strains isolated from urinary specimens received from general practitioners it was found that in about half of the cases it was possible to trace the isolated Klebsiella type to a hospital to which the patient had been admitted at an earlier date.

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GLUTAMIC ACID IN HEPATIC COMA

By ERIK WESTENGAARD, HANS-GEORG IVERSEN & VAGN LARSEN

HISTORICAL

Walshe (1) and Richardson & Moffatt (2) drew attention to the treatment of hepatic coma with glutamic acid.

Walshe was probably the first to demonstrate that glutamic acid can relieve the comatose condition. He treated 3 comatose patients with glutamic acid and observed favourable effect in all cases as all the patients woke and became fully conscious, even after prolonged coma (4—8 days).

Two of his patients were alive when his work went to press, viz. 14 months and 1 month after the conclusion of the treatment while one patient died in coma at home after the elapse of 8 months; treatment had not been instituted on this occasion. All three were clear cases of cirrhosis. In two of the cases the coma occurred as deterioration of the condition while the third developed in connection with porta-caval anastomosis.

Richardson & Moffatt record one case of coma which developed in connection with porta-caval anastomosis in which glutamic acid administered orally produced immediate good effect.

Priest, Whitehead & Whittaker (6) similarly record one case. Glutamic acid was administered via a duodenal tube after coma lasting for 4 days and the effect was excellent.

In a paper concerning the mechanism of action of glutamic acid, Singh, Barclay & Cooke (3) briefly mention 3 patients suffering from coma and treated with glutamic acid. These authors observed good effect in one patient while in the other two patients no effect was observed.

In the Department of Surgery, Finseninstitutet, we have just treated a patient suffering from hepatic coma with glutamic acid intravenously. The effect was, in our opinion, characteristic and striking:

From the Department of Surgery, Finseninstitutet. Surgeon-in-Charge: *A. Zacho.*

CASE HISTORY

Female, aged 58 years (case history No. Z 1829); married. The patient had previously been healthy and, in particular, never suffered from hepatitis.

One year prior to admission, the patient developed distention of the abdomen, the circumference of which gradually increased considerably. When the condition had been present for 6 months, the patient was admitted to a surgical department elsewhere where the diagnosis of ascites and occult cancer was made. Exploratory laparotomy was undertaken but no tumour was revealed. Macroscopic signs of cirrhosis of the liver were, however, present and biopsy showed chronic hepatitis and cirrhosis.

Following operation, paracentesis of the abdomen was performed an several occasions with the removal of large quantities of ascitic fluid.

Shortly before admission to this department, massive oedema of the lower extremities developed together with increasing ascites, while the appetite failed and the general condition deteriorated. The patient was admitted for investigation in view of possible porta-caval anastomosis.

On admission, the condition of the patient was, however, far too poor for operation. Definite ascites was present; oedema of the lower limbs; distinctly reduced liver function; icteric index 5; B.S.R. 22 mm/hour; distinct erythema of the palms.

Despite conservative treatment with low salt, low fat, protein rich and carbohydrate rich diet, vitamins (A, B, C and K) in large doses, Hepsol (liver extract containing vitamin B_{12}) together with transfusions of blood and serum, the condition deteriorated.

After the elapse of 3 weeks during which the general condition fluctuated but was, as a rule,

poor, definite deterioration occurred. The patient became increasingly apathetic, drowsy and tired, the appetite diminished and she drank very little; the diuresis became small and faeces and urine were voided involuntarily; the patient became difficult to contact and finally completely comatose.

The plasma electrolytes, including sodium and potassium, were all within practically normal limits, while the icteric index rose (7-10-15). Blood urea rose to 94 mg./% but fell again to 30 mg./% although the condition did not improve. The excretion of sodium in the urine fell while the potassium excretion increased, probably an

Table I.

Date:	5/4	6/4	7/4	8/4	9/4	10/4	11/4	12/4	13/4	14/4
Coma:	+	+	+	—	—	+	+	+	—/+	death
Days of Treatment:			1.	2.	3.	4.	5.	6.	7.	8.
Haemoglobin %	90	93	91	83	75	78	73	79	84	80
Erythrocytes mill/cmm	3.90	4.00	4.55	3.40	3.60			4.20	3.80	4.00
Haematocrit %	39	37	37	36	32			33	37	37
Serum protein %	7.1	6.6	6.9	6.4	6.4			7.0	7.3	7.5
Blood urea mg/%	90	69	30	83	94	82	102	110	98	127
Serum chloride mEq/l.	81	81	83	80	80			75	71	73
Serum bicarbonate mEq/l.	22	22	21	28	27	31	35	40	39	38
Plasma sodium mEq/l.	126	124	122	130	128			138	140	136
Plasma potassium mEq/l.	4.8	4.0	4.1	4.0	3.9			2.1	2.3	2.6
Magnesium mg/%			2.3							
Urinary sodium mEq/l.	8		2	2	2		12	16	4	
Urinary potassium mEq/l.	17		29	41	68		61	128	56	
Urinary urea gr.			0.612	1.344	1.288	1.840	1.400	1.872	1.224	
Plasma colour	15		17	20	15	17		17	35	35
Amino-N mg/%			8.0	8.6	8.6					

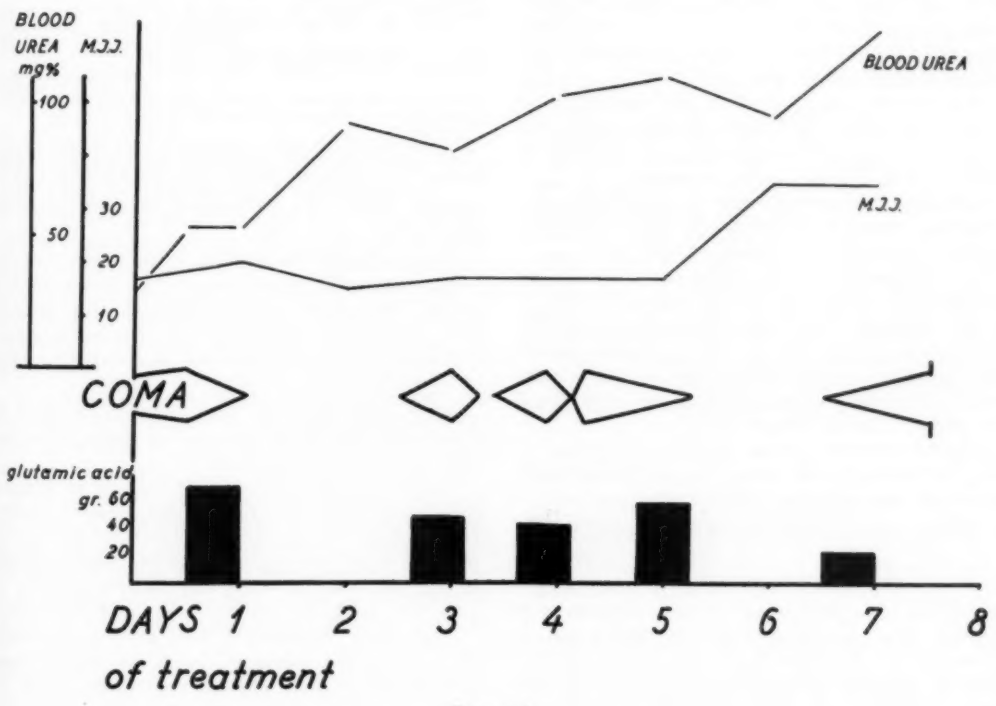

Figure 1.

M. I. I. = Meulengracht's icteric index.

The condition of coma is indicated by diverging lines when the condition deteriorated clinically and by converging lines when the condition improved clinically.

expression of the fact that the patient was under considerable »stress« (see table I).

After nearly two days of deep unconsciousness, administration of glutamic acid (23 gm. glutamic acid neutralized by sodium hydroxide, dissolved in 500 ml. 6 % glucose solution) was instituted; a total of 69 gm. was given as slow intravenous drip. The infusion was commenced at 12.45 p. m. and continued until 12 midnight (see Figure 1).

At 1.30 a. m. the patient began to recover consciousness; she spoke spontaneously, recognized the surroundings and later in the day she was able to read a newspaper. She complained, however, of fatigue.

The condition remained unchanged for 42 hours, after which the patient became comatose again. Glutamic acid was administered once more (a total of 46 gm.); shortly thereafter, the patient recovered consciousness.

Six hours later she again became comatose. Intravenous administration of amino acid mixture was attempted first (Aminacid) but this failed to wake the patient; on the contrary, the stupor increased. When this condition had lasted for 12 hours, glutamic acid was again resorted to but after 43 gm. had been administered, the infusion had to be interrupted on account of venous stasis and threatening pulmonary oedema. At this point, the patient was awakening but after the interruption of treatment she became more confused again. The heart was stimulated with Cedilanid (pure glucoside of digitalis, Sandoz) and treatment with Theophylamin suppositories was commenced in order to attempt to reduce the massive oedema which was present in the loins and the lower limbs. After the elapse of some hours, the circulation improved somewhat and infusion of glutamic acid (58 gm.) was resumed.

Gradually, the patient woke up completely, was conscious, orientated, spoke naturally with those around her but was extremely tired.

This continued for 36 hours, after which the condition of coma supervened again. A total of 23 gm. glutamic acid was administered but on account of venous stasis, tissue oedema (probably caused by sodium retention) and pulmonary oedema, further therapy had to be abandoned. The patient died 24 hours later.

Autopsy showed: portal hepatic cirrhosis, ascites, left hydrothorax, atelectasis of the left lung, peritoneal concretions, moderate hyperplasia of the spleen and atherosclerosis of the aorta.

EXPERIMENTS

Prior to the treatment of the patient with glutamic acid, we undertook the following experiments to ascertain if a comatose condition could be induced in mice by injecting them with serum from the patient and, if so, whether this condition could be influenced by treatment with glutamic acid.

Five 2 months old Bagg-albino male mice were injected intraperitoneally with serum from the comatose patient, receiving 0.1, 0.2, 0.4, 0.6 and 1.0 ml. respectively.

Five other mice received serum from the same patient protected by paraffin in view of possible volatile toxic substances.

In both groups, gradual reduction of spontaneous activity was observed 3 minutes after the injection; the animals became sleepy and lethargic and sought the corners of the cage where they could only be roused by rather violent mechanical irritation. On the other hand, they reacted very strongly and abnormally to auditory stimulation as, when the sides of the cage were struck with a forceps, the mice performed extraordinary jerking movements. These were of quite short duration and developed simultaneously in all the affected animals. Fits and actual coma were not observed and there was no difference between the animals which received the least and those which received the largest doses of serum.

Five control animals which received the same doses of serum from a healthy individual did not show any changes in the spontaneous activity nor abnormal reactions to auditory stimulation.

¾ hour after the injection of the serum from the patient, the animals in both groups which had received 0.2 and 0.6 ml. serum received 0.5 ml. sodium glutamate solution intraperitoneally. No rousing effect attributable to this injection could be observed.

Both the untreated and the treated animals in both experimental groups began to revive after 2 hours had elapsed since the commencement of the experiment and after 5 hours they were quite normal.

To investigate if ammonia were an etiological factor in the production of unconsciousness in hepatic coma, we performed the following experiment:

Young Bagg-albino male mice were injected intraperitoneally with increasing doses of 0.15 molar ammonium lactate solution (the solution was formed by adding 15 gm. 90 % lactic acid and 10.2 gm. 25 % ammonium hydroxide to 1 litre of water).

After absorption of this solution it must be presumed that the lactic acid is metabolized and that ammonia is liberated.

Following the injection, all degrees of lethargy appeared in the mice until coma occurred following a dose of approximately 1.25 ml. 10—20 minutes after the injection. If the dose exceeded 2 ml., the animals died but otherwise they recovered completely in the course of 2—3 hours.

The reflex irritability was greatly increased, showing at the commencement the same strange »jerks« as in the serum experiment when the animals were exposed to auditory stimulation. Later, generalized clonic and tonic fits occurred spontaneously but these were also easily released by all forms of mechanical irritation.

Control experiments showed that mice of the same weight (approximately 15 gm.) could tolerate 4 ml. physiological saline injected intraperitoneally without inconvenience.

To investigate the effect of sodium glutamate on this induced condition, the following experiment was performed:

Five Bagg-albino male mice, each weighing 15 gm., received 1 ml. sodium glutamate intraperitoneally. Five other mice received 1 ml. physiological saline. 15 minutes later all of them received 1.5 ml. of a solution of ammonium lactate and from 10—15 minutes after this injection, those animals which had received physiological saline became comatose and had frequent fits; one animal died during a prolonged fit. Those animals which had received sodium glutamate were, on the other hand, only moderately drowsy; one, however, became stuporose.

Preliminary injection of sodium glutamate prevented the ocurrence of coma in all the animals.

If, however, the sequence was altered so that the solution of sodium glutamate was administered after the animals had gone into coma under the influence of ammonium lactate, no definite rousing effect was observed.

DISCUSSION

The actual cause of the condition of coma in liver insufficiency and also the effect of glutamic acid on this is unknown.

One or several of the following causes are conceivable:

1. On account of disturbed protein metabolism, accumulation of ammonia occurs to 6—10 times the normal extent (6) which exerts a toxic effect with predominately cerebral manifestations.

The effect of glutamic acid may here be conceived to be that together with ammonia it forms urea which is then excreted (cf. the falling blood urea level at the beginning of the coma and the increasing blood urea level following administration of glutamic acid and the clinical improvement).

Walshe is of the opinion that glutamic acid combines with ammonia to form glutamine and that glutamine is catabolized without the formation of ammonia.

Singh et al. (3) demonstrated that glutamic acid had a reducing effect on ammonia in the blood in 3 out of their 4 patients treated with glutamic acid but these authors are, however, of the opinion that ammonia is not an etiological factor in the development of coma, cf. that increased values for blood ammonia are found following porta-caval anastomosis, which is in agreement with Kirk's observations (5).

2. Glutamic acid is the only amino acid which can be metabolized in the brain. It may be conceived that deficiency of this amino acid may injure the brain with resulting unconsciousness (1).

3. According to Weil-Malherbe (4) the effect of glutamic acid depends on the fact that it is essential for the enzyme reactions: desamination, transamination and amidizing, all reactions which effect the removal of intracellular ammonia. This assumption is supported by the increased amino acid-N which is found in hepatic coma.

4. Finally, it may be conceived that glutamic acid is an essential factor in the carbohydrate metabolism by mediating the catabolism of pyruvic acid, cf. that increased values for pyruvic acid may be found during coma (2) and that the brain mainly metabolizes carbohydrates.

5. Possibly a combination of these factors or a factor as yet unknown.

Our patient should probably have received glutamic acid during the entire course of the illness, e. g. as tablets only. The condition was so poor that it was considered impossible to administer the massive doses involved by any other route than the intravenous. In this manner, the general condition was influenced to such an extent that treatment had to be interrupted.

SUMMARY

A case of hepatic coma in a female aged 58 years with cirrhosis of the liver and treated with sodium glutamate is recorded. It was possible to relieve the comatose condition several times and in a way which suggests that a definite relation between the infusion of glutamic acid and the recovery from the comatose condition exists.

In experiments on mice, a condition of lethargy was produced by injection of the patient's serum intraperitoneally, but this was not relieved by glutamic acid. On the other hand it was demonstrated that, by injection of a solution of ammonium lactate intraperitoneally in mice, a condition of coma may be produced and that this comatose condition may be prevented by prophylactic treatment with sodium glutamate. Once coma has developed, no definite rousing effect of sodium glutamate is observed.

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THE EFFECT OF D-AMPHETAMINE ON OBESE CHILDREN

By

HENNING ANDERSEN and *FLEMMING QUAADE*

In 1937 several workers (Ulrich, Nathanson, and others) noted loss of weight in persons receiving amphetamine for narcolepsy. Since then, a number of reports have been published — mainly by American authors — on the effect of amphetamine and amphetamine-like substances in animal experiments (Ehrich and Krumbhaar 1937, Searle and Brown 1938, Harris et al. 1947), in experiments on non-obese persons (Davidoff and Reifenstein 1937, Davidoff 1943, Harris et al. 1947) and in the treatment of obese adults (Lesses and Myerson 1938, Rosenberg 1938, Colton et al. 1943, Hawirko and Sprague 1946, Coopersmith 1949, Freed 1949, Gelvin and McGavack 1949, Roberts 1951). These reports show that the racemic amphetamine sulphate(DL-form, »benzedrine«) as well as the dextro-rotary isomer (D-amphetamine sulphate, »dexedrine«) may induce weight loss. The mechanism is a reduction in appetite with a consequently reduced intake of food. Increased muscular activity plays a small role as is apparent from human experiments conducted by Harris et al., who simultaneously with the administration of amphetamine and despite the anorexia maintained a constant, rather high caloric intake. Moreover, the anorexigenic effect of D-amphetamine appears to be about twice that of racemic amphetamine. The details of their mechanism are not yet definitely elucidated, but the anorexigenic effect in dogs remains unchanged after the stomach and upper part of the small intestine have been denervated by bilateral vagotomy and splanchno-lumbar sympathectomy. It is also known that patients who develop morbid hunger (bulimia) following frontal lobotomy are less responsive to D-amphetamine than other subjects. Harris et al., therefore, presume that the anorexigenic effect of the drugs is not due to an effect on the motility of the gastro-intestinal tract, but that they affect the central appetite regulation — in the cerebrum and possibly also in the hypothalamus. These authors checked their patients with a view to factors as varied as the red blood count, white blood count, hemoglobin level, fasting blood sugar, glucose tolerance, glucosuria, proteinuria, serum ascorbic acid, serum phophatase, passage through the intestines, and blood pressure — without finding any divergences from normal. In a series of 105 adult patients with obesity Freed (1949) found that side effects such as nervousness, nausea, headache, palpitations, and dryness of the mouth hardly occurred in persons on D-amphetamine, while one or more of these complaints were present in nearly one-third of the patients treated with the DL-form. Constipation developed in about one in every six patients in both groups. Davidoff (1943), studying the effect of the drugs in a small series of normal and depressed persons, states that insomnia and irritability are often caused by D-amphetamine, whereas actual euphoria is most marked and most common in patients receiving racemic amphetamine.

Many of the adult series, however, suffer from the drawback that the treatment has not been carried out with amphetamine alone. The anorexigenic drugs have been combined with other measures, such as dietary restriction, thyroid preparations, mercury diuretics, and theophylline. Many authors have also failed to run control series.

Kunstadter (1940) reported weight loss in 30 obese children after treatment with benzedrine; and also Bruch and Waters (1942) have suggested benzedrine in the treatment of obese children. Later, Mossberg and Frisk (1950) conducted a major study on the effect of D-amphetamine as an adjuvant in the dietetic treatment of obesity in childhood. They treated 167 obese children by dietary restriction and gave, in addition, every other child D-amphetamine 2½ mg three times daily, while the others received placebo tablets of the same appearance and in the same doses. The combined loss of weight in the two groups was calculated on the basis of Rohrer's index. The group treated with D-amphetamine showed a more marked average fall in the index than the group treated with placebos. The difference was significant, at least during the first five months of the treatment. Side effects were rare and negligible.

There were several reasons why we felt that further studies on the effect of D-amphetamine on obese children would be desirable, even after Mossberg and Frisk's report har been published. In the first place, we wanted to observe the effect of D-amphetamine when administered as the only therapeutic agent, without any restric-

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tion of the diet. In the second place, we were anxious to exclude any element of suggestion which might influence the patients' response to the agent and thereby the results of the investigation. By the procedure used by Mossberg and Frisk, the physician knew which of the tablets were active and which were placebos. We dared not exclude that the energy with which one would enjoin the patients to observe the prescribed diet would unconsciously become influenced by one's knowledge as to whether a given child was being treated by diet alone or by a combination of diet and a pharmacologically active substance. We also wanted to observe the effect of individualized doses of D-amphetamine and not of a standard dosage which might be too high for at small child or, conversely, insufficient for at big child. Finally, the study was motivated by a wish to get acquainted with an agent which might contribute to the solution of the big therapeutic problem presented by the obesity of childhood in this country.

On the basis of these considerations, we conducted our study as follows:

All obese children who attended the Clinic for Endocrine Disorders at the Queen Louise Children's Hospital from the summer of 1952 to the summer of 1953 were treated with tablets. Every other child received D-amphetamine and the others placebo tablets of exactly the same appearance. The two types of tablets were marked by a faked name, known only to the manufacturing chemist who supplied them. The dosage was adapted to body weight according to the following table.

Table 1.

Dosage of D-amphetamine and placebo.

Weight, kg.	mg daily:
under 25	2.5
25—30	5.0
30—35	7.5
35—40	10.0
40—45	12.5
45—50	15.0
50—55	17.5
55—60	20.0
60—65	22.5
65—70	25.0
70—75	27.5
75—80	30.0
over 80	32.5

In a few cases where no weight loss had occurred after two months's treatment, the dose was increased by about one-third. Whenever possible, the dose was fractionated into several daily doses administered prior to the main meals, the last dose not, however, later than 4 or 5 p. m.

The children totalled 103 and ranged in age from 4 to 16 years. All were indubitably obese, with overweights ranging from 1.4 to 8.7 times the dispersion on the weights in the height groups concerned. The majority had overweights between 2.5 and 4.0 times the dispersion (as to the calculation of the degree of overweight, cf. Quaade 1954). At the ontset, the patients were checked once weekly, later at 2, 3, and in some cases at 4 week intervals. The blood pressure and pulse rate were controlled, and the children as well as their parents questioned regarding any side effects. It was strongly emphasized that the dosage had to be observed and that the parents, particularly the mothers, must not interfere with the children's food intake, whether they found it too small or too large. It was soon evident that a small proportion of the series (6 patients) had to be ruled out, because an effective dietary restriction was being practised at home. A somewhat larger group had to be excluded, because it was admitted that the children forgot to take the tablets (15 patients) or because the children failed to appear for the follow-up after a period so short (less than one month) that the result could not be properly estimated (11 patients). The great majority of the excluded patients belonged to the placebo group, which thus was reduced to a considerably smaller number than the group treated with the active drug. One child proved to have myxoedema and was therefore also left out of the series.

This leaves 70 children, 25 boys and 45 girls, who took tablets for aggregate periods ranging from 1 to 11 months, usually from 2 to 8 months. The majority of the patients tried both kinds of tablets, so that the analysis comprises a total of 74 treatments with D-amphetamine and 43 with placebo.

For each patient we recorded the weight in a coordinate system giving the type of tablet as well as the child's sex, age, and height. Out of the 70 resulting graphs, 58 disclosed a convincing effect of D-amphetamine; eight showed some, but not quite definite effect, and only four children failed to respond to treatment with active substance. Figs. 1 and 2 set out 8 of the »successful«, 2 of the doubtful experiments, and 2 »failures«.

Table 2 gives a survey of alle the individual weight losses during the administration of D-amphetamine and placebo respectively. It is clear that in the former group the weight losses are far more frequent and more marked than in the placebo group. Summation of the weight changes within the two groups shows that the boys treated with placebos gained a total of 9.4 kg in the course of about 50 months, whereas the boys in the D-amphetamine group have lost a total of 93.8 kg at the and of about 103 months' treatment. The corresponding figures for the girls are a gain of 24.6 kg after about 70 months' administration of placebos and a loss of 182.6 kg after about 215 months' treatment with D-amphetamine.

The average initial weight of the boys and girls in the placebo groups were 1.0 and 1.4 kg respectively lower than those in the D-amphetamine

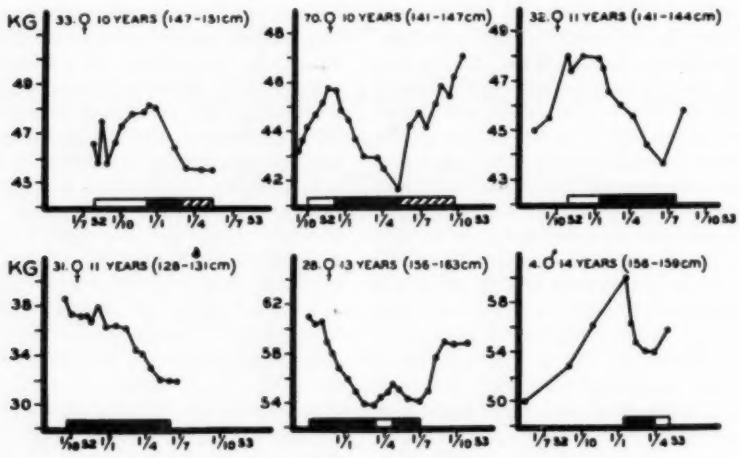

Fig. 1.

6 therapeutic experiments showing good conformity between weight loss and D-amphetamine medication.

White: Placebo. Black: D-amphetamine. Shaded: Dose of D-amphetamine not observed regularly.

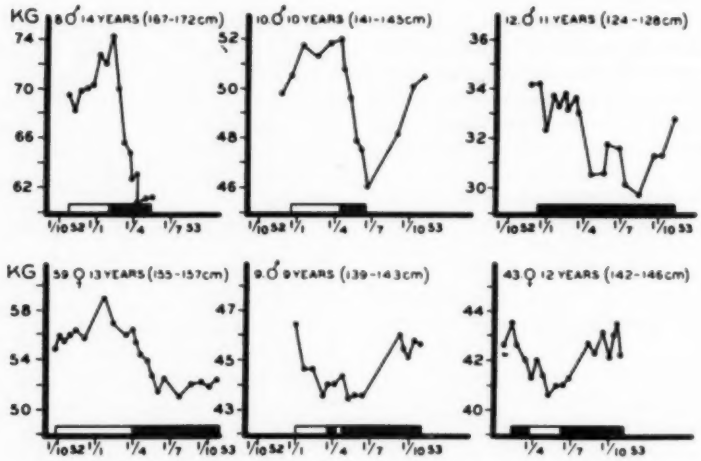

Fig. 2.

The first two curves show good effect of D-amphetamine. Case 12: Initial weight loss replaced by weight gain despite continued D-amphetamine medication. In Case 59 the weight had begun decreasing before D-amphetamine was started. Case 9: Weight loss on placebo, gain on D-amphetamine. Case 43: Weight loss during the first period of D-amphetamine, weight loss on placebo, predominantly weight gain the second period of D-amphetamine.

groups. Classification of the materials according to initial weight, however, shows that this does not influence the total result, the children treated with D-amphetamine, unlike those given placebos, losing weight within *all* weight groups (Table 3).

As to the reasons why a few children lost weight on the placebo tablets we can only surmise. In most cases it was probably because despite our request, the diet was restricted at home. The explanation of why a few children did not lose weight during treatment with D-amphetamine is presumed to be in most cases failure to take the tablets, although we could not make the children admit it. In other cases the reason was perhaps an increased tolerance of the drug. This presumption is supported by the fact that a satisfactory effect in such cases was observed after the dose had been increased by about one-third.

Table 2.

Survey of individual and total weight loss during treatment of 70 obese children (25 boys and 45 girls) with D-amphetamine and/or placebo.

BOYS

Case	Placebo Weight loss, kg	Months	D-Amphetamine Weight loss, kg	Months
1	65.5—64.0=1.5	2¼	64.0—58.3= 5.7	5
2			64.6—56.2= 8.4	7½
3			57.3—53.5= 3.8	2¼
4	54.0—55.9=—1.9	1¼	60.0—54.0= 6.0	2½
5	42.7—42.5=0.2	5		
6	32.2—30.6=1.6	3¼	30.6—31.8=—1.2	2¾
7	42.6—41.0=1.6	1	45.3—39.4= 5.9	3
8	69.5—74.2=—4.7	3¼	74.2—61.1=13.1	3¼
9	46.5—44.1=2.4	2½	44.1—44.1= 0	½
—	44.1—44.4=—0.3	¾	44.4—45.7=—1.3	6¼
10	50.5—52.0=—1.5	4	52.0—46.0= 6.0	2
—			50.1—50.4=—0.3	¾
11	46.3—48.5=—2.2	2¼	49.7—45.4= 4.3	8
12			34.2—32.8= 1.4	11
13	69.1—70.0=—0.9	4	66.0—64.6= 1.4	2¼
14			48.9—46.8= 2.1	½
15	47.4—49.5=—2.1	5	49.5—43.8= 5.7	5½
16	41.6—43.3=—1.7	2	43.3—41.8= 1.5	3
17	52.7—53.0=—0.3	3	53.0—45.3= 7.7	2
18			46.2—39.5= 6.7	5
19	54.7—55.8=—1.1	5¼		
21			38.9—35.4= 3.5	4½
22			31.5—28.7= 2.8	4½
23			91.3—88.6= 2.7	2¼
24			48.2—44.3= 3.9	7½
25			46.8—42.8= 4.0	9
	Total —9.4	47½	Total 93.8	102¼

GIRLS

Case	Placebo Weight loss, kg	Months	D-Amphetamine Weight loss, kg	Months
20	39.8—39.8=0	2¾	39.8—39.8= 0	1½
26			36.9—34.6= 2.3	2¼
—			36.3—34.8= 1.5	¾
27			43.0—33.0=10.0	11¼
28	54.0—55.6=1.6	7½	66.1—54.0= 7.1	5¼
—			55.6—54.2= 1.4	2
29			57.7—54.9= 2.8	3½
30			39.3—38.3= 1.0	6
31			38.6—31.8= 6.8	8½
32	48.0—47.9=0.1	2½	47.9—44.9= 3.0	6
33	46.6—48.2=—1.6	4½	48.2—45.6= 2.6	3
34	57.2—61.6=—4.4	1½	58.3—57.2= 1.1	6
—			61.6—58.4= 3.2	1½
35			21.5—18.9= 2.6	8
36	33.2—36.0=—2.8	2¾	36.0—35.3= 0.7	¾
—	35.3—35.8=—0.5	¼	35.8—34.2= 1.6	2½
37	44.7—44.2=0.5	4½		
38			55.6—50.0= 5.6	2¼
39			76.3—73.0=3.3	6¼
40			62.2—52.0=10.2	4½
41			48.8—44.8= 4.0	7¼
42			42.6—37.1= 5.5	9½
43	41.3—41.0=0.3	2½	43.5—41.3= 2.2	1½
—			41.0—42.2=—1.2	4½
44	40.0—43.7=—3.7	4¼	43.7—39.5= 4.2	3½
45			52.6—51.5= 1.1	5½
46			50.2—42.8= 7.4	4½
47	65.5—65.1=0.4	3¼		
48	49.5—49.6=—0.1	2¾		
—	51.1—51.6=—0.5	½	51.6—46.3= 5.3	2
49			38.0—35.4= 2.6	2½
50			36.5—32.2= 4.3	2¾
51	42.2—44.3=—2.1	3	44.3—40.8= 3.5	8
52			61.7—56.2= 5.5	3¼
53			42.5—37.5= 5.0	4
—	37.5—38.3=—0.8	¾	38.3—37.5= 0.8	1¼
54	74.0—72.8=1.2	3¼	72.8—65.6= 7.2	4
55	50.0—51.6=—1.6	3¼	51.6—49.6= 2.0	1¼
—	49.6—50.0=—0.4	¼	50.0—49.0= 1.0	5
56	49.5—49.0=0.5	7¾	49.0—48.7= 0.3	1½
57	42.5—42.8=—0.3	1	42.8—39.1= 3.7	4
58			42.5—40.0= 2.5	6
59	55.0—56.5=—1.5	6¼	56.5—52.4= 4.1	7
60			76.6—67.0= 9.6	6
61			36.0—31.7= 4.3	8¼
62	50.0—51.8=—1.8	3¼	51.8—48.2= 3.6	1½
—	48.2—50.1=—1.9	¼	50.1—49.5= 0.6	5
63			44.4—36.5= 7.9	3
64			70.0—67.4= 2.6	9½
65	48.8—50.3=—1.5	1½		
66	56.9—57.2=—0.3	1	59.0—56.9= 2.1	3
67	41.2—40.2=1.0	3¾	40.2—39.0= 1.2	1¼
68	31.8—31.5=0.3	2½		
69			59.4—50.4= 9.0	4
70	44.1—45.6=—1.5	2¼	45.6—41.7= 3.9	5
	Total —24.6	70¾	Total 182.6	215¼

Nearly all the children stated spontaneously that their appetite had decreased perceptibly after they had begun taking the D-amphetamine tablets.

In 20 cases side effects were recorded during the treatment with D-amphetamine. The total number of untoward symptoms was 26. As seen from Table 4, the most common complaint was difficulty in falling asleep at night. This, however, subsided in a few days — usually spontaneously — but in a few cases not until the patients began taking the last tablet at a somewhat earlier hour in the afternoon. All the other side effects disappeared spontaneously in the course of a few days, and in no case was it necessary to reduce the dosage or withdraw the drug. In three instances it was reported that the placebo tablets had given rise to side effects — insomnia, irritability, and unrest — and the mother of a fourth child informed us that the placebo tablets were better for cough than D-amphetamine.

To sum up:

D-amphetamine in the doses used causes marked weight loss in the great majority of obese children.

This weight loss is presumably due exclusively to an anorexigenic effect.

Table 3.

Material classified according to weight at commencement of treatment. Weight loss and periods of treatment are considered together for patients in the same sub-group. Weight gain marked by negative sign.

BOYS

Initial weight kg	Placebo				D-Amphetamine			
	Number of treatments	Weight loss kg	Period of treatment (months)	Weight loss kg/mnth	Number of treatments	Weight loss kg	Period of treatment (months)	Weight loss kg/mnth
20—30	—	—	—	—	1	2.6	8	0.3
30—40	2	1.6	6	0.3	5	6.5	24½	0.3
40—50	7	—2.1	18½	—0.1	10	32.8	48½	0.7
50—60	4	—4.8	13½	—0.4	4	17.2	7	2.5
60—70	3	—4.1	9½	—0.4	4	21.5	17¼	1.2
70—	—	—	—	—	2	15.8	5½	2.9
Total	16	—9.4	47½	—0.2	25	93.8	102¼	0.9

GIRLS

Initial weight kg	Placebo				D-Amphetamine			
	Number of treatments	Weight loss kg	Period of treatment (months)	Weight loss kg/mnth	Number of treatments	Weight loss kg	Period of treatment (months)	Weight loss kg/mnth
30—40	4	— 3.8	6¼	—0.6	10	25.9	35½	0.7
40—50	14	—10.7	40¾	—0.3	16	58.3	79¼	0.7
50—60	7	—11.7	17¼	—0.7	14	47.1	52½	0.9
60—70	1	0.4	3¼	0.1	4	26.0	14½	1.8
70—	1	1.2	2¼	0.4	4	22.7	25¾	0.9
Total	27	24.6	70¾	—0.3	49	182.6	215½	0.9

Table 4.

Side effects of D-amphetamine in boys and girls.

Side effect:	Boys:	Girls:
Difficulty in fallling asleep	4	7
Restless sleep	3	1
Irritability, unrest, restlessness	2	3
Constipation	1	2
Stomach-ache	1	1
Fatigue	0	1
Pallor	0	0
Palpitations	0	0
Change in blood pressure	0	0
Change in pulse rate	0	0
Habituation	0	0
Abstinence symptoms	0	0
Total	11	15

Side effects — which occurred in less than one-third of our cases — were so slight and transitory as to be negligible.

This paper is not concerned with the permanent results of treatment with D-amphetamine or with its place in the treatment of obese children. The lines which we feel we can recommend in this respect, int. al. with regard to a combination of dietary restriction and anorexigenic drugs, will be the subject of a subsequent communication.

The D-amphetamine was kindly supplied, through Ferrosan Ltd., Copenhagen, by the Smith, Kline & French Laboratories, Philadelphia.

In the statistical work we were assisted by N. F. Gjeddebæk, actuary.

We acknowledge our indebtedness to all those who have contributed to the performance of this study.

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A DISPOSABLE INFUSION SET

K. H. KØSTER

In 1949 the Scandinavian Countries agreed on a Standard Infusion Equipment (1), which has been used in Denmark for one million infusions.

The Scandinavian (INSTA) equipment consists of a bottle and an infusion set, based on the two-cannula principle. The bottle is closed with a rubber bung pierced by two holes. The combined drip-filter is made of a glass chamber, two rubber stoppers and a nylon filter. It is fitted with a metal cannula piercing the rubber bung of the bottle. Air is let into the bottle by a similar cannula, connected with a length of rubber tubing, and a similar tube, preferably latex, leads to the patient.

When the filter chamber etc. is to be re-used it is carefully cleansed, assembled, packed and sterilized. This procedure, plus renewal of the expendable parts such as nylon filter, rubber stoppers and latex tubing, plus the collection and distribution af the sets, costs approximately the equivalent af ten shillings.

In spite of very careful handling by the blood bank some pyrogenic reactions occurred. It is probably quite impossible to clean a used, soft and sticky latex tube so as to get rid of all pyregenic matter.

In order to avoid complications arising from previous use and contamination, a disposable set was constructed.

The disposable set (Fig. 1 an 2) is of INSTA dimensions, and it consists of an egg-shaped nylon house containing a horizontal nylon filter, about 10 sq. centimeters, fitted with two piercing cannulas, and connexions for air inlet and infusion tube, both made af glass clear plastic.

It will also fit any other bottle which is closed by a rubber stopper or diaphragm.

The complete set is wrapped in paper, packed into a cardboard box, sterilized and delivered ready for use (Fig. 1).

From Bispebjerg Hospital, Surg. Department A.
Chief Surgeon: *Jens Foged,* M. D.

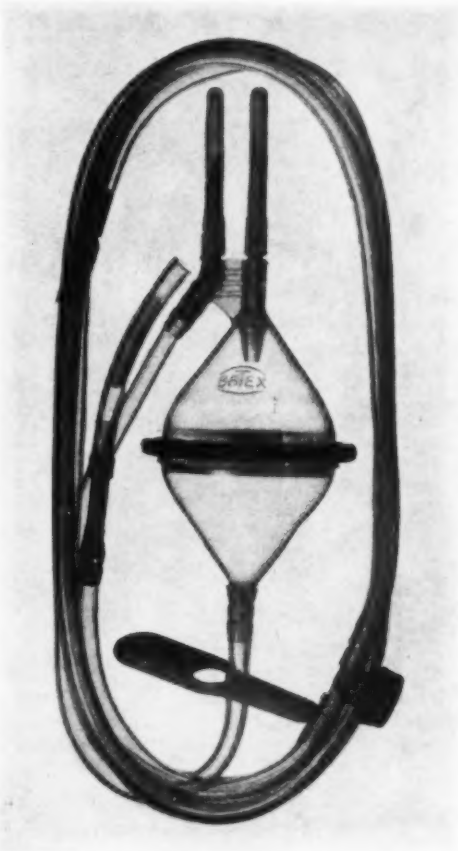

Fig. 1.
The infusion set unwrapped.

The coverings should be removed from the cannulas and the needle adapter, the coils of the tube unfolded, and the infusion set should be attached to the bottle as shown in fig. 2.

It will be noted that the coils of the tube adhere slightly, so that no single parts are dropping out when the pack is opened.

The filter has a capacity af more than 1.000 ml of blood in ten minutes, as proposed by the International Standards Organization as a minimum requirement.

It is virtually impossible to take the set to pieces, and no one would feel tempted to clean and use it again. When used the whole set, filter, tube and all is discarded. Complications arising from previous use and contamination are thus eliminated.

At Bispebjerg Hospital, Copenhagen, approximately 8.000 disposable sets have been used since january 1954, and no ill effects have been recorded.

The costs of using these disposable sets — which is the salient point — is estimated to about half of the expenditure for preparation and maintenance of the ordinary sets.

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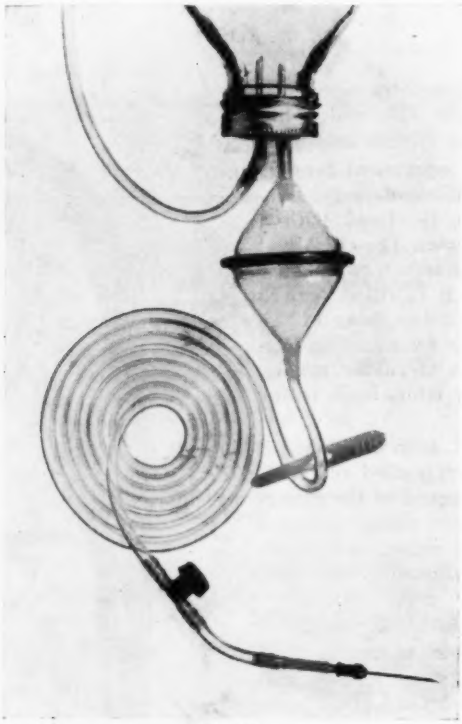

Fig. 2.
The disposable set in situ.

The set consists of an egg-shaped drop chamber containing a horizontal filter, and a glass clear plastic tube (180 cm) leading to the needle adapter which will fit Record *and* Luer hub. An injection tube (2) with a thick rubber diaphragm permits injection of drugs etc. into the plastic tube. During the infusion the fluid should cover the filter.

The disposalle set is manufactured by Bang & Tegner, Copenhagen.